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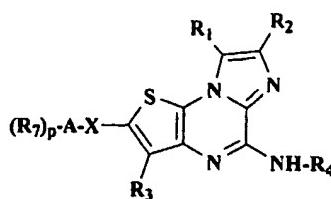
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(54) Title: THIOPENE-BASED TRICYCLIC COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS COMPRISING
SAME



(I)

(57) Abstract: Compounds having the formula (I), and pharmaceutically-acceptable salts, hydrates and prodrugs thereof, are useful as anti-inflammatory agents, in which R1, R2, and R3 are hydrogen, halogen, alkyl, or perfluoroalkyl; R4 is an optionally substituted alkyl or cycloalkyl group; X is a linker; A is an aryl, heteroaryl, heterocycle, cycloalkyl, or is absent; and R7 is a substituent on A as defined in the specification.

THIOPHENE-BASED TRICYCLIC COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS COMPRISING SAME

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Field of the Invention

The present invention relates to thiophene-based tricyclic compounds, to methods of using the compounds in treating inflammatory and immune diseases, and to pharmaceutical compositions comprising same.

10

Background of the Invention

Tumor necrosis factor (TNF- α) is a potent cytokine having pro-inflammatory properties that is released by many cell types when stimulated. Studies have shown a relationship between elevated levels of TNF- α and a variety of diseases such as septic shock, hematopoiesis, tumors, and inflammatory disorders of the central nervous system, including HIV encephalitis, cerebral malaria, and meningitis. Certain neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Creutzfeldt-Jacob disease also are reportedly associated with enhanced TNF- α levels. See, e.g., Arvin *et al.*, "The Role of Inflammation and Cytokines in Brain Injury," Neuroscience and Biobehavioral Reviews, Vol. 20, No. 3 (1996), at pp. 445-452.

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Accordingly, various classes of drugs have been researched and developed to inhibit TNF- α production at both transcriptional and translational levels, e.g., corticosteroids, rolipram (a phosphodiesterase IV inhibitor suppressing TNF- α mRNA synthesis), calphostin, and imidazole-type cytokine suppressing anti-inflammatory drugs (CSAIDs). These drugs are useful in treating a variety of diseases. See Dinarello, "Role of Pro- and Anti-Inflammatory Cytokines During Inflammation: Experimental and Clinical Findings, Review, Vol. 0393-974X (1997), at pp. 91-103.

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Recently, attention has focussed on the role of Nuclear factor κ B (NF- κ B) in the activation pathway that leads to production of TNF- α and other inflammatory cytokines and gene types. Besides TNF- α , NF- κ B is involved in the regulation of a variety of genes involved in immune function and inflammation, including IL-2, IL-6, IL-8, IL-

2R α , GM-GSF, intercellular adhesion molecule (ICAM-1), and vascular cellular adhesion molecule-1 (VCAM-1). Thus, inhibition of NF- κ B and/or its activation pathway provides a means for treating various diseases including autoimmune diseases, Alzheimer's disease, atherosclerosis, oncogenesis, and so forth. See, e.g., Baldwin, "*The NF- κ B and I κ B Proteins: New Discoveries and Insights*," *Annual Rev. Immunol.*, Vol. 14 (1996), at pp. 649-81; see also Christman *et al.*, "*Impact of Basic Research on Tomorrow's Medicine, The Role of Nuclear Factor- κ B in Pulmonary Diseases*," *Chest*, Vol. 117 (2000), at pp. 1482-87.

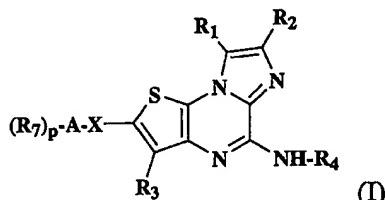
Potential inhibitors of the NF- κ B and/or the NF- κ B pathway have been identified as including Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants. I κ B is a cytoplasmic protein that controls NF- κ B activity by retaining NF- κ B in the cytoplasm. I κ B is phosphorylated by the I κ B kinase (IKK), which has two isoforms, IKK- α ("IKK-1") and IKK- β ("IKK-2"). When IKK phosphorylates I κ B, NF- κ B is rapidly released from the cytoplasm into the cell. Upon release into the cell, NF- κ B translocates to the nucleus where it binds to the promoters of many genes and up-regulates the transcription of pro-inflammatory genes. Glucocorticoids reportedly inhibit NF- κ B activity by two mechanisms, *i.e.*, upregulating I κ B protein levels and inhibiting NF- κ B subunits. Nitric oxide also reportedly inhibits NF- κ B through upregulation of I κ B. However, these mechanisms of interaction are complex; for example, production of nitric oxide in lymphocytes reportedly enhances NF- κ B activity.

As may be appreciated, those in the field of pharmaceutical research continue to seek to develop new compounds and compositions having increased effectiveness, bioavailability, and solubility, having fewer side effects, and/or providing the consumer with a choice of options. Particularly in the area of immune response, many individuals respond differently depending upon the type of treatment and chemical agent used. Mechanisms of action continue to be studied to aid in understanding the immune response and in developing compounds effective for treating inflammatory and immune-related disorders.

The present invention provides thiophene-based tricyclic compounds useful as inhibitors of IKK. Pyrrolothioenopyrazines having binding affinity for 5-HT₃ receptors are disclosed in Rault *et al.*, J. Med. Chem., Vol. 39 (1996), at pp. 2068-80, and European patent application No. 573,360 (12/8/93). A broad genus of compounds including certain aromatic-substituted tricyclic thiophenes is disclosed in WO 94/05665 to Neurogen Corp. for use as GABA brain receptor ligands. Polycyclic thiophene compounds are also disclosed in GB Pat. Appl. 2,344,818 to Pharmacia and Upjohn (6/21/00), WO 00/35428 to Boehringer Ingelheim (6/22/00), EP Pat. Appl. 1,104,764 to Hokuriku Seiyaku Co. (6/6/01), and Cardoso *et al.*, Bioorg. Med. Chem. Lett., Vol. 12 (2002), at pp. 9-12. AstraZeneca (WO 01/58890, 8/16/01) reported that certain monocyclic, amide-substituted thiophene compounds may be useful as IKK inhibitors.

Summary of the Invention

The invention is directed to compounds of formula (I), useful in treating inflammatory or immune conditions:



enantiomers, diastereomers, pharmaceutically-acceptable salts, and solvates thereof,
in which:

R₁, R₂, and R₃ are independently selected from hydrogen, halogen, alkyl, and perfluoroalkyl;
R₄ is -(CR₅R₆)_m-Z or -(cycloalkyl)-Z;
R₅, R_{5a}, R₆ and R_{6a} at each occurrence are independently selected from hydrogen, alkyl, substituted alkyl, amino, alkylamino, substituted alkylamino, hydroxy, alkoxy, substituted alkoxy, cycloalkyl, heterocycle, aryl, and heteroaryl;

- R₇ at each occurrence is selected independently of each other R₇ from alkyl, substituted alkyl, alkenyl, substituted alkenyl, halogen, cyano, -(CR_{5a}R_{6a})_q-OR_{8a}, -(CR_{5a}R_{6a})_q-SR_{8a}, -(CR_{5a}R_{6a})_q-SO₂R₁₀, -(CR_{5a}R_{6a})_q-NR₈R₉, -(CR_{5a}R_{6a})_q-NR₈SO₂, -(CR_{5a}R_{6a})_q-NR₈SO₂R₁₀, -(CR_{5a}R_{6a})_q-SO₂NR₈R₉, -(CR_{5a}R_{6a})_q-NR_{8a}C(=O)R_{9a},
- 5 -(CR_{5a}R_{6a})_q-NR_{8a}CO₂R_{9a}, -(CR_{5a}R_{6a})_q-C(=O)R_{8a}, -(CR_{5a}R_{6a})_q-CO₂R_{8a}, -(CR_{5a}R_{6a})_q-OC(=O)R_{8a}, -(CR_{5a}R_{6a})_q-C(=O)NR₈R₉, -(CR_{5a}R_{6a})_q-CO₂NR₈R₉, -(CR_{5a}R_{6a})_q-OC(=O)NR₈R₉, -(CR_{5a}R_{6a})_q-C(=O)NR_{8a}-NR₈R₉, -(CR_{5a}R_{6a})_q-C(=O)NR_{8a}SO₂R₁₀, -(CR_{5a}R_{6a})_q-NR_{8a}C(=O)NR₈R₉, -(CR_{5a}R_{6a})_q-NR_{8a}SO₂NR₈R₉, -(CR_{5a}R_{6a})_q-NR_{8a}C(=O)-C(=O)-NR₈R₉,
- 10 -(CR_{5a}R_{6a})_q-NR_{8a}C(=O)-CO₂R_{9a}, -(CR_{5a}R_{6a})_q-N(SO₂R₁₀)(SO₂R_{10a}), -(CR_{5a}R_{6a})_q-OSO₂NR₈R₉, cycloalkyl, (cycloalkyl)alkyl, heterocycle, (heterocyclo)alkyl, aryl, (aryl)alkyl, heteroaryl, and (heteroaryl)alkyl, or when A is heterocycle or cycloalkyl, one of R₇ may be keto (=O), and when A is a bond, then R₇ may be hydrogen;
- 15 X is a bond, O, S, -NR₁₁-, -(CH₂)_n-, -CH=CH-, or -C≡C-; A is a bond, aryl, heteroaryl, heterocycle, or cycloalkyl; Z is selected from hydrogen, methyl, OR₁₄, -C(=O)OR₁₄, -NR₁₂C(=O)R₁₃, -NHC(=NR_{14a})R_{15a}, -NR₁₂CO₂R₁₃, -NR₁₂SO₂R₁₃, -C(=O)NR₁₄R₁₅, -NR₁₄R₁₅ and -NR₁₂-C(=O)NR₁₄R₁₅;
- 20 R₈ R_{8a}, R₉ and R_{9a} are independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, (cycloalkyl)alkyl, heterocycle, (heterocyclo)alkyl, aryl, (aryl)alkyl, heteroaryl, and (heteroaryl)alkyl; or R₈ and R₉ together with the nitrogen atom to which they are bonded may combine to form a heterocyclo ring;
- 25 R₁₀ and R_{10a} are independently alkyl, substituted alkyl, cycloalkyl, heterocycle, aryl, or heteroaryl; R₁₁ is hydrogen, alkyl, aminoalkyl, or hydroxyalkyl; R₁₂ is hydrogen or lower alkyl; R₁₃ is hydrogen, alkyl, substituted alkyl, cycloalkyl, heterocyclo, aryl or heteroaryl;

R_{14} R_{14a} , R_{15} and R_{15a} are independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycle, (heterocylo)alkyl, aryl, (aryl)alkyl, heteroaryl, and (heteroaryl)alkyl;

or R_{14} and R_{15} together with the nitrogen atom to which they are bonded may combine to
5 form a heterocyclo ring;

m and q are independently 0, 1, 2, 3, 4, 5 or 6;

n is 1 or 2; and

p is 0, 1, 2, 3 or 4, except when A is a bond, then p is 1.

10 The invention also relates to pharmaceutical compositions containing at least one compound of formula (I) and a pharmaceutically-acceptable carrier or diluent, for use in treating inflammatory and immune diseases. Also included within the invention are methods of treating such diseases comprising administering to a mammal in need of such treatment an effective amount of at least one compound of formula (I).

15

Detailed Description of the Invention

The following are definitions of terms used in this specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated.

20

The term "alkyl" refers to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. Lower alkyl groups, that is, alkyl groups of 1 to 4 carbon atoms, are most preferred. When numbers appear in a subscript after the symbol "C", the subscript defines with more specificity the number of carbon atoms that a particular group may contain. For example, " C_{1-6} alkyl" refers to straight and branched chain alkyl groups with one to six carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, and so forth. When the subscript "0" is used, as in C_0 , this refers to a bond. Thus, the term C_{0-2} hydroxyalkyl refers to hydroxy, hydroxymethyl, and hydroxyethyl.

The term "substituted alkyl" refers to an alkyl group as defined above having one, two, or three substituents selected from the group consisting of halogen, trifluoromethyl, alkenyl, alkynyl, nitro, cyano, keto (=O), haloalkoxy, -OR, -SR, -NRR', -NRSO₂R', -SO₂R", -SO₂NRR', -CO₂R, -C(=O)R, -C(=O)NRR', -OC(=O)R, -OC(=O)NRR', -NRC(=O)R', -NRC(=O)-NRR', -NRCO₂R', =N-OH, =N-O-alkyl, aryl, heteroaryl, 5 heterocyclo and cycloalkyl, wherein R and R' are selected from hydrogen, alkyl, alkenyl, amino, alkylamino, substituted alkylamino, cycloalkyl, (cycloalkyl)alkyl, heterocycle, (heterocyclo)alkyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, (alkoxy)alkyl, (CO₂H)alkyl, (NC(=O)R)alkyl, (hydroxy)alkyl, (amino)alkyl, (alkylamino)alkyl, or R and R' together may form a heterocyclo or heteroaryl ring, and R" is alkyl, alkenyl, 10 benzyl, phenylethyl, cycloalkyl, heterocyclo, aryl, and/or heteroaryl. When an alkyl is substituted with an aryl, heteroaryl, heterocyclo or cycloalkyl, those groups are as recited below and thus optionally may be substituted as recited below. Each of R, R', and R" in turn may have zero to three substituents (preferably 0-2 substituents), selected from 15 halogen, alkyl, haloalkyl, alkenyl, nitro, cyano, -OH, -O(alkyl), haloalkoxy, hydroxyalkoxy, aminoalkoxy, phenyl, benzyl, phenylethyl, phenoxy, benzyloxy, -SH, -S(alkyl), -S(phenyl), -NH₂, -NH(alkyl), -N(alkyl)₂, -NH(cycloalkyl), -NHSO₂(alkyl), -SO₂(alkyl), -SO₂NH₂, -SO₂NH(alkyl), -SO₂N(alkyl)₂, -CO₂H, -CO₂(alkyl), -C(=O)H, -C(=O)alkyl, -C(=O)NH₂, -C(=O)NH(alkyl), -C(=O)N(alkyl)₂, -OC(=O)alkyl, 20 -OC(=O)NH₂, -OC(=O)NH(alkyl), -OC(=O)N(alkyl)₂, -NHC(=O)alkyl, -NHCO₂(alkyl), C₃₋₇cycloalkyl, C₅₋₆heteroaryl, and C₄₋₇heterocyclo.

When the term alkyl is used as a suffix with a second named group, as in arylalkyl or cycloalkylalkyl, this refers to a substituted alkyl in which at least one of the substituents is the second named group. For example, the term arylalkyl includes benzyl 25 and any other straight or branched chain alkyl having at least one aryl group attached at any point of the alkyl chain. Other substituents may be attached to the alkyl chain or the second named group. Such substituents may be selected as appropriate from the groups recited above in the definition of substituted alkyl and/or from those recited herein for the second named group.

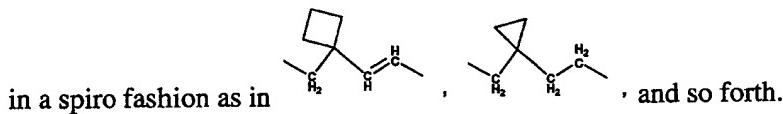
The term "alkenyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one double bond. Alkenyl groups of 2 to 6 carbon atoms and having one double bond are most preferred. Alkenyl groups may be optionally substituted as described in the definition of "substituted alkyl".

5 The term "alkynyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and at least one triple bond. Alkynyl groups of 2 to 6 carbon atoms and having one triple bond are most preferred.

10 The term "alkylene" refers to bivalent straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms, *e.g.*, $\{-\text{CH}_2-\}_n$, wherein n is 1 to 12, preferably 1-8. Lower alkylene groups, that is, alkylene groups of 1 to 4 carbon atoms, are most preferred. The terms "alkenylene" and "alkynylene" refer to bivalent radicals of alkenyl and alkynyl groups, respectively, as defined above.

When reference is made to a substituted alkylene, alkenylene, or alkynylene, these groups are substituted with one to three substituents as defined above for alkyl groups.

15 A substituted alkylene, alkenylene, or alkynylene may have a ringed substituent attached



20 The term "alkoxy" refers to the group $-\text{OR}$, wherein R is alkyl or alkenyl. The term "alkylthio" refers to the group $-\text{SR}$, wherein R is alkyl or alkenyl. The term "alkylamino" refers to the group $-\text{NR}'\text{R}''$, wherein each of R' and R'' is selected from hydrogen, alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocyclo, as defined herein, provided that both R' and R'' are not hydrogen. The term "amino" refers to $-\text{NH}_2$. A substituted alkoxy, alkythio, or alkylamino may have zero to three substituents as defined above for substituted alkyl.

25 When a subscript is used with an alkoxy, alkylthio or alkylamino, the subscript refers to the number of carbon atoms that the group may contain in addition to heteroatoms. Thus, for example, monovalent $\text{C}_{1-2}\text{alkylamino}$ includes the groups $-\text{NH}-\text{CH}_3$, $-\text{NH}-\text{CH}_2-\text{CH}_3$, and $-\text{N}(\text{CH}_3)_2$. A lower alkylamino comprises an alkylamino having one to four carbon atoms.

The alkoxy, alkylthio, or alkylamino groups may be monovalent or bivalent. By “monovalent” it is meant that the group has a valency (*i.e.*, power to combine with another group), of one, and by “bivalent” it is meant that the group has a valency of two. For example, a monovalent alkoxy includes groups such as -O-C₁₋₁₂alkyl, whereas a 5 bivalent alkoxy includes groups such as -O-C₁₋₁₂alkylene-, etc.

The term “acyl” refers to a carbonyl {-C(=O)-} linked to an organic group

i.e., $\begin{array}{c} \text{O} \\ || \\ \text{—C}—\text{R} \end{array}$, wherein R may be selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, heterocyclo, cycloalkyl, and heteroaryl, as defined herein.

The term “alkoxycarbonyl” refers to a carboxy or ester group {-CO₂-} linked to

10 an organic radical, *i.e.*, $\begin{array}{c} \text{O} \\ || \\ \text{—C}—\text{O—R} \end{array}$, wherein R is as defined for acyl. “Carboxy” refers to the group CO₂H, and “carboxyalkyl” refers to -R-CO₂H, wherein R is alkylene or substituted alkylene.

15 The term “carbamyl” refers to a functional group in which a nitrogen atom is directly bonded to a carbonyl, *i.e.*, as in -NRC(=O)R’ or -C(=O)NRR’, wherein R and R’ can be hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, cycloalkyl, aryl, heterocyclo, or heteroaryl.

The term “heteroatoms” shall include oxygen, sulfur and nitrogen.

The term “haloalkyl” means an alkyl having one or more halo substituents and thus includes, for example, trifluoromethyl.

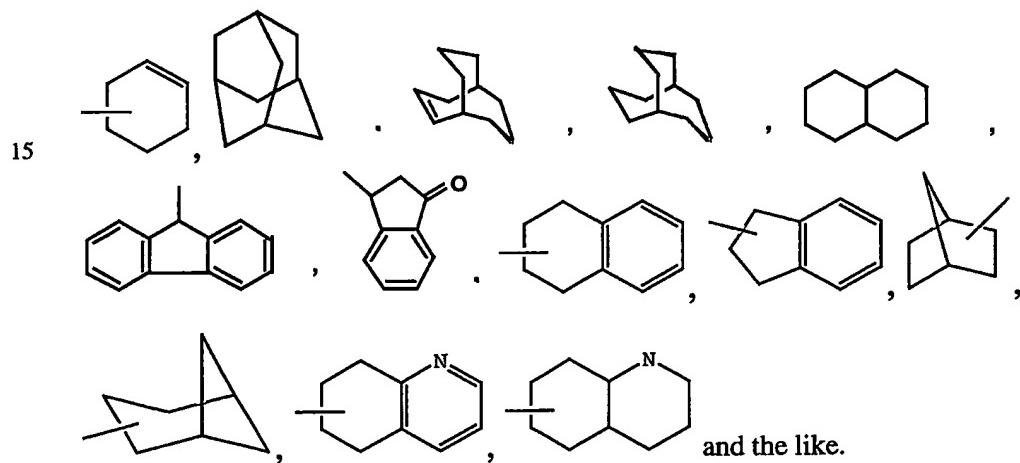
20 The term “perfluoroalkyl” means an alkyl group having from one to five fluoro atoms, such as pentafluoroethyl. The term “perfluoromethyl” means a methyl group substituted by one, two, or three fluoro atoms, *i.e.*, CH₂F, CHF₂ and CF₃.

The term “haloalkoxy” means an alkoxy group having one or more halo substituents. For example, “haloalkoxy” includes -OCF₃.

25 The term “sulfonyl” refers to a sulphoxide group (*i.e.*, -S(O)₁₋₃) linked to an organic radical R”, wherein R” is alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, heterocyclo, heteroaryl, or aryl. Sulfonic acid is -SO₃H.

The term "sulfonamide" or "sulfonamido" refers to the group $-\text{S}(\text{O})_2\text{NRR}'$, wherein R and R' are selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, heterocyclo, heteroaryl or aryl. Preferably when one of R and R' is optionally substituted cycloalkyl, heterocyclo, heteroaryl or aryl (as defined below), the other of R and R' is hydrogen or alkyl.

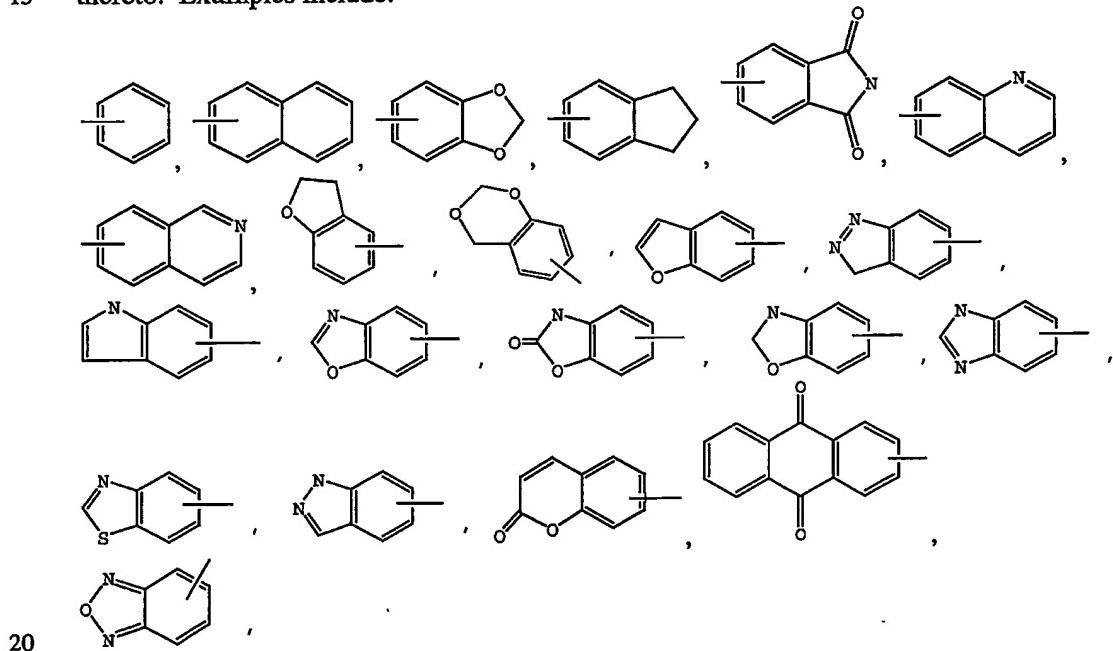
The term "cycloalkyl" refers to fully saturated and partially unsaturated substituted or unsubstituted hydrocarbon rings of 3 to 20, preferably 3 to 7 carbon atoms. Cycloalkyl ring systems include monocyclic, bicyclic and tricyclic rings. The rings of multi-ring cycloalkyls may be either fused, bridged and/or joined through one or more spiro union to 1 or 2 aromatic, cycloalkyl or heterocyclo rings. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, cycloheptadienyl,



When substituted, the cycloalkyl will contain one to three (preferably one to two) groups selected from alkyl, halogen, perfluoroalkyl, alkenyl, alkynyl, nitro, cyano, keto ($=\text{O}$), haloalkoxy, $-\text{OR}$, $-\text{SR}$, $-\text{NRR}'$, $-\text{NRSO}_2\text{R}'$, $-\text{SO}_2\text{R}''$, $-\text{SO}_2\text{NRR}'$, $-\text{CO}_2\text{R}$, $-\text{C}(\text{=O})\text{R}$, $-\text{C}(\text{=O})\text{NRR}'$, $-\text{OC}(\text{=O})\text{R}$, $-\text{OC}(\text{=O})\text{NRR}'$, $-\text{NRC}(\text{=O})\text{R}'$, $-\text{NRCO}_2\text{R}'$, $=\text{N}-\text{OH}$, $=\text{N}-\text{O-alkyl}$, phenyl, 3 to 6 membered heteroaryl or heterocyclo, and/or C_3 -cycloalkyl, wherein R and R' are independently selected from hydrogen, alkyl, alkenyl,

phenyl, benzyl, phenylethyl, C₃₋₇cycloalkyl, and 3 to 6 membered heterocyclo or heteroaryl, and R" is alkyl, alkenyl, phenyl, benzyl, phenylethyl, C₃₋₇cycloalkyl, and/or 3 to 6 membered heterocyclo or heteroaryl. The term "cycloalkyl" also includes such rings having a phenyl ring fused thereto or having a carbon-carbon bridge of 3 to 4 carbon atoms. Additionally, when a cycloalkyl is substituted with a further ring, *i.e.*, phenyl, benzyl, etc., such ring in turn may be substituted with one to two C₀₋₄alkyl optionally substituted with (or linked to) one to two of halogen, CF₃, OCF₃, alkenyl, nitro, cyano, keto (=O), hydroxy, alkoxy, SH, S(alkyl), NH₂, NH(alkyl), N(alkyl)₂, CO₂H, CO₂(alkyl), C(=O)H, and/or C(=O)alkyl.

The terms "ar" or "aryl" as used herein by itself or as part of another group refer to aromatic homocyclic (*i.e.*, hydrocarbon) monocyclic, bicyclic or tricyclic aromatic groups containing 6 to 14 carbons in the ring portion (such as phenyl, biphenyl, naphthyl (including 1-naphthyl and 2-naphthyl) and anthracenyl) and may optionally include one to three additional rings (either cycloalkyl, heterocyclo or heteroaryl) fused thereto. Examples include:



and the like. Preferred aryl groups include phenyl and naphthyl, with phenyl being generally more preferred.

The term "aryl" includes such rings having zero to three substituents (preferably 0-2 substituents). When substituted, the aryl ring will contain one to three groups independently selected from alkyl, halogen, perfluoroalkyl, alkenyl, alkynyl, nitro, cyano, haloalkoxy, -OR, -SR, -NRR', -NRSO₂R', -SO₂R'', -SO₂NRR', -CO₂R,
5 -C(=O)R, -C(=O)NRR', -OC(=O)R, -OC(=O)NRR', -NRC(=O)R', -NRCO₂R', phenyl, 3 to 6 membered heteroaryl or heterocyclo, and C₃₋₇cycloalkyl, wherein R and R' are independently selected from hydrogen, alkyl, alkenyl, phenyl, benzyl, phenylethyl, C₃₋₇cycloalkyl, or 3 to 6 membered heterocyclo and heteroaryl, and R'' is alkyl, alkenyl, phenyl, benzyl, phenylethyl, C₃₋₇cycloalkyl, and/or 3 to 6 membered heterocyclo or
10 heteroaryl. Additionally, two substituents attached to an aryl, particularly a phenyl group, may join to form a further ring including a spiro ring or a fused ring, *e.g.*, spirocyclopentyl or fused cyclohexenyl, or fused heteroaryl or heterocyclo. When an aryl is substituted with a further ring, such ring in turn may be substituted with one to two C₀₋₄alkyl optionally substituted with (or linked to) one to two of halogen, CF₃, OCF₃,
15 alkenyl, nitro, cyano, keto (=O), hydroxy, alkoxy, SH, S(alkyl), NH₂, NH(alkyl), N(alkyl)₂, CO₂H, CO₂(alkyl), C(=O)H, and/or C(=O)alkyl.

The term "heterocyclo" refers to substituted and unsubstituted non-aromatic 3 to 7 membered monocyclic groups, 7 to 11 membered bicyclic groups, and 10 to 15 membered tricyclic groups, in which at least one of the rings has at least one heteroatom
20 (O, S or N). Each ring of the heterocyclo group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms, provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom and no two adjacent heteroatoms are simultaneously selected from -O- and -S-. The fused rings completing bicyclic and tricyclic groups
25 may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The heterocyclo group may be attached at any available nitrogen or carbon atom. The heterocyclo ring may contain zero to three substituents independently selected from alkyl, halogen, perfluoroalkyl, alkenyl, alkynyl, nitro, cyano,
30 haloalkoxy, =O, =NR, -OR, -SR, -NRR', -NRSO₂R', -SO₂R'', -SO₂NRR', -CO₂R,

–C(=O)R, –C(=O)NRR', –OC(=O)R, –OC(=O)NRR', –NRC(=O)R', –NR₂CO₂R', aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, heterocyclo, (heterocyclo)alkyl, cycloalkyl and/or (cycloalkyl)alkyl, wherein R and R' are independently selected from hydrogen, alkyl, alkenyl, phenyl, benzyl, phenylethyl, C₃-cycloalkyl, and 3 to 6 membered heterocyclo or heteroaryl, and R" is alkyl, alkenyl, phenyl, benzyl, phenylethyl, C₃-cycloalkyl, or 3 to 6 membered heterocyclo or heteroaryl. The term "heterocyclo" also includes such rings having a phenyl ring fused thereto or having a carbon–carbon bridge of 3 to 4 carbon atoms. Additionally, when a heterocyclo is substituted with a further ring, such ring in turn may be substituted with one to two C₀₋₄alkyl optionally substituted with (or linked to) one to two of halogen, CF₃, OCF₃, alkenyl, nitro, cyano, keto (=O), hydroxy, alkoxy, SH, S(alkyl), NH₂, NH(alkyl), N(alkyl)₂, CO₂H, CO₂(alkyl), C(=O)H, and/or C(=O)alkyl.

Exemplary monocyclic groups include oxiranyl, aziridinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, and the like. Exemplary bicyclic heterocyclo groups include quinuclidinyl.

The term "heteroaryl" refers to substituted and unsubstituted aromatic 5 to 7 membered monocyclic groups, 9 or 10 membered bicyclic groups, and 11 to 14 membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms, provided that the total number of heteroatoms in each ring is four or less, each ring has at least one carbon atom, and no two adjacent heteroatoms are simultaneously selected from –O– and –S–. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring, but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl

group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may contain zero to three substituents (preferably 0-2 substituents), selected from C₀₋₆alkyl optionally substituted with (or linked to) one to two of halogen, perfluoroalkyl, alkenyl, alkynyl, nitro, cyano, haloalkoxy, keto (=O), -OR, -SR, -NRR', -NRSO₂R', -SO₂R'', -SO₂NRR', -CO₂R, -C(=O)R, -C(=O)NRR', -OC(=O)R, -OC(=O)NRR', -NRC(=O)R', -NRCO₂R', phenyl, 3 to 6 membered heteroaryl or heterocyclo, and/or C₃₋₇cycloalkyl, wherein R and R' are independently selected from hydrogen, alkyl, alkenyl, phenyl, benzyl, phenylethyl, C₃₋₇cycloalkyl, and 3 to 6 membered heterocyclo or heteroaryl, and R'' is alkyl, alkenyl, phenyl, benzyl, phenylethyl, C₃₋₇cycloalkyl, and/or 3 to 6 membered heterocyclo or heteroaryl.

10 Additionally, when a heteroaryl is substituted with a further ring, such ring in turn may be substituted with one to two C₀₋₄alkyl optionally substituted with (or linked to) one to two of halogen, CF₃, OCF₃, alkenyl, nitro, cyano, keto (=O), OH, O(alkyl), phenoxy, benzyloxy, SH, S(alkyl), NH₂, NH(alkyl), N(alkyl)₂, CO₂H, CO₂(alkyl), C(=O)H, and/or C(=O)alkyl.

15

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, indazolyl, benzothiazolyl, benzodioxolyl, benzoxaxolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl, dihydroisoindolyl, and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzidolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The term "carbocyclic" means a saturated or unsaturated monocyclic or bicyclic ring in which all atoms of all rings are carbon. Thus, the term includes cycloalkyl and aryl rings. The carbocyclic ring may be substituted in which case the substituents are selected from those recited above for cycloalkyl and aryl groups, as appropriate.

When the term "unsaturated" is used herein to refer to a ring or group, the ring or group may be fully unsaturated or partially unsaturated.

Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds.

5 The compounds of formula I form salts which are also within the scope of this invention. Reference to a compound of the formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of formula I contains both a basic moiety, such as,
10 but not limited to an amine or a pyridine ring, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful, *e.g.*, in isolation or purification steps which may be employed during preparation. Salts of the
15 compounds of the formula I may be formed, for example, by reacting a compound of the formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates (such as those formed with acetic
20 acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid),
25 hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed

with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines [formed with N,N-bis(dehydroabietyl)ethylenediamine], N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

Compounds of the formula I, and salts thereof, may exist in their tautomeric form, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the invention. Additionally, inventive compounds may have *trans* and *cis* isomers and may contain one or more chiral centers, therefore existing in enantiomeric and diastereomeric forms. The invention includes all such isomers, as well as mixtures of *cis* and *trans* isomers, mixtures of diastereomers and racemic mixtures of enantiomers (optical isomers). When no specific mention is made of the configuration (*cis*, *trans* or R or S) of a compound (or of an asymmetric carbon), then any one of the isomers or a mixture of more than one isomer is intended. The processes for preparation can use racemates, enantiomers, or diastereomers as starting materials. When enantiomeric or diastereomeric products are prepared, they can be separated by conventional methods, for example, by chromatographic or fractional crystallization. The inventive compounds may be in the free or hydrate form.

In addition, compounds of formula I may have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, a compound of formula I) is a prodrug within the scope and spirit of the invention.

- For example, pro-drug compounds of formula I may be carboxylate ester
5 moieties. A carboxylate ester may be conveniently formed by esterifying any of the carboxylic acid functionalities found on the disclosed ring structure(s). Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:
- 10 a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985), and Methods in Enzymology, Vol. 42, at pp. 309-396, edited by K. Widder, *et. al.* (Academic Press, 1985);
b) A Textbook of Drug Design and Development, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, “*Design and Application of Prodrugs*,” by H. Bundgaard, at pp. 113-191 (1991);
c) H. Bundgaard, Advanced Drug Delivery Reviews, Vol. 8, p. 1-38 (1992);
15 d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, Vol. 77, p. 285 (1988); and
e) N. Kakeya, *et. al.*, Chem Phar Bull, Vol. 32, p. 692 (1984).

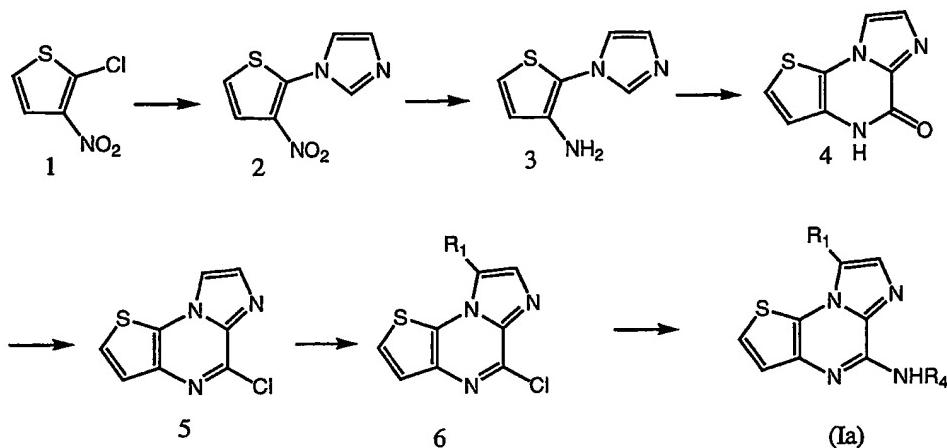
It should further be understood that solvates (*e.g.*, hydrates) of the compounds of formula I are also within the scope of the present invention. Methods of solvation are
20 generally known in the art.

Methods of Preparation

The inventive compounds may be prepared by methods such as those illustrated in the following Schemes I to VII. Starting materials are commercially available or can be
25 readily prepared by one of ordinary skill in the art, and/or modifications can be made to the methods of Schemes I to VII by one skilled in the art, using known methods. For all of the schemes and compounds, the groups R₁, R₂, R₄, R₆ and R₇ are as described herein for a compound of formula I, unless otherwise indicated, and appropriate starting materials may be selected by one skilled in the field having the desired groups. Solvents,
30 temperatures, pressures, and other reaction conditions may readily be selected as

appropriate by one of ordinary skill in the art. For example, in these schemes chlorinating agents may include phosphorous oxychloride, catalytic agents may include metals such as Pd, and solvents may be selected from 1,2-dichlorobenzene, methylene chloride, DMF, alcohols, ethers, THF, dioxane, acetonitrile, water, mixtures of ethers and water, and the like.

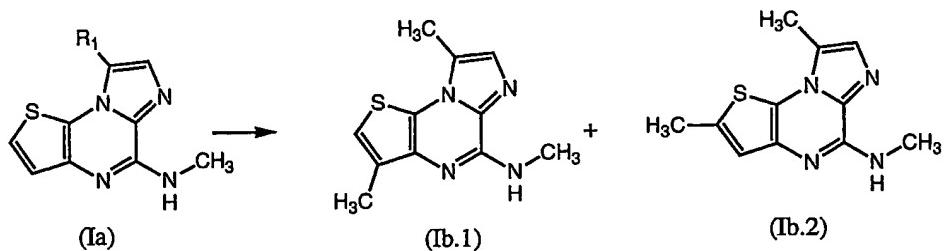
"Cross-coupling" or coupling reactions as used in the schemes and examples may include all cross-coupling methods known by those skilled in the art. Such methods include Stille-type coupling (reacting a vinyl or aromatic triflate, bromide or iodide with a tin), Suzuki-type coupling (reacting a zinc, magnesium or boronate derivative catalyzed by palladium(0), palladium(II), nickel(0) or nickel(II)), Heck coupling, and Sonogashira coupling. Copper iodide, lithium chloride, zinc chloride, triphenylarsine, tris(2-furyl)phosphine or tris(2,4,6-trimethoxyphenyl)-phosphine advantageously may also be added. When a boronic acid derivative is used, the reaction may proceed in the presence of an inorganic base such as sodium carbonate or potassium phosphate or carbonate. The cross-coupling reactions are performed in an inert organic solvent.

Scheme I

5

Compounds 5 can be prepared from 2-chloro-3-nitro-thiophene 1 by a route established in the literature for making imidazo[1,2-a]quinoxalines. (See J. Med. Chem., Vol. 34 (1991) at p. 2671). For example, 2-chloro-3-nitro-thiophene 1 can be converted to 2 upon treatment with imidazole in DMF; compounds 2 can be hydrogenated in a solvent such as MeOH to provide 3; compounds 3 can be cyclized to 4 upon treatment in *o*-dichlorobenzene with 1,1'-carbonyldiimidazole; and compounds 4 can be converted to 5 upon treatment with N,N-diethylaniline and POCl₃.

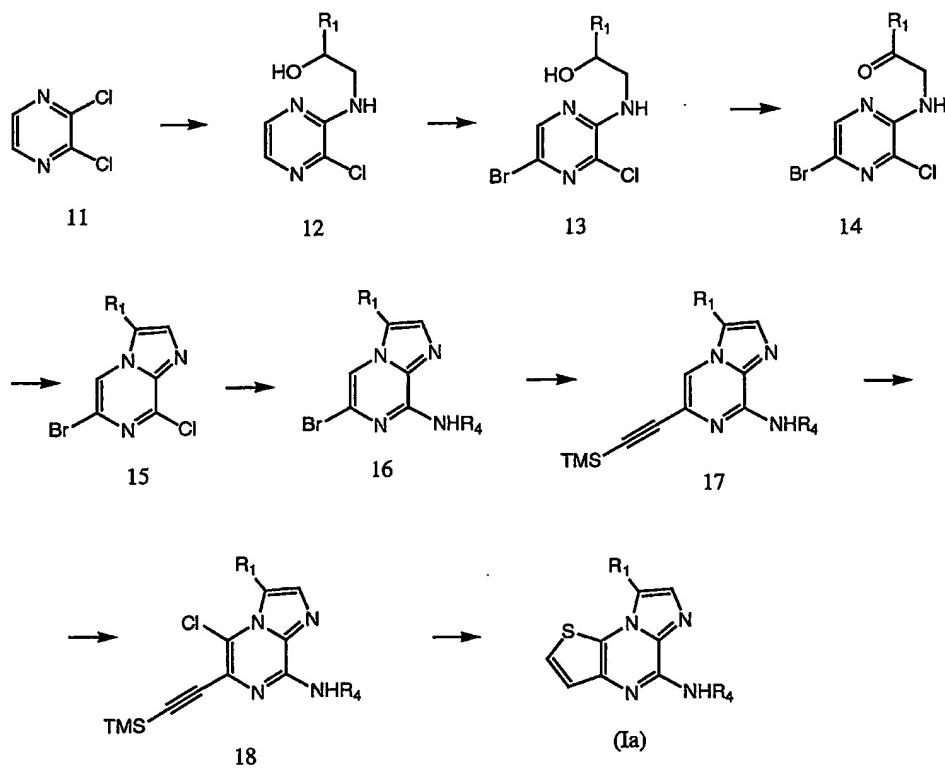
Compounds 6 wherein R₁ is bromo or chloro can be prepared from compounds 5 by halogenation with *N*-chlorosuccinimide or *N*-bromosuccinimide in a solvent such as THF. Compounds of formula (Ia) can be prepared from compounds 6 by aminolysis with an appropriate alkylamine (NH₂R₄) in a solvent such as THF.

Scheme II

Compounds (Ia) (wherein R₁ is CH₃) can serve as a starting point for further functionalization of the thienoimidazopyrazine core structure. For example, compounds (Ib.1) and (Ib.2) can be prepared from (Ia) (wherein R₁ is CH₃) via lithiation followed by iodomethane quenching.

Scheme III

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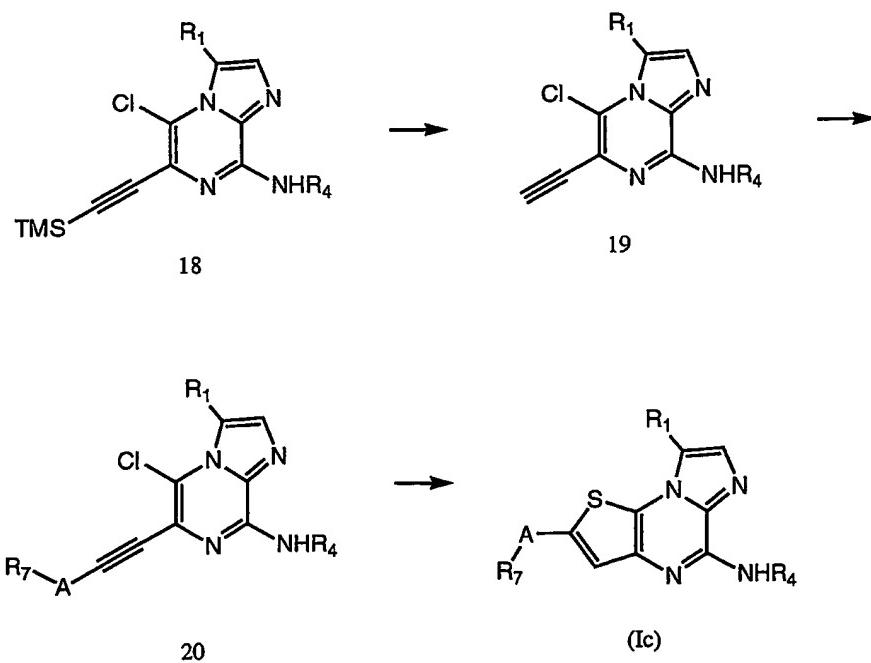


19

Scheme III shows an alternative route to Scheme I for making compounds of formula (Ia). Compounds of formula (Ia) can be prepared by cyclization of chloro compounds 18, e.g., upon treatment with Na₂S·9H₂O in a solvent such as DMF. Chloro compounds 18 can be prepared from compounds 17 by chlorination with *N*-chlorosuccinimide in THF. Alkynes 17 can be prepared by performing Sonogashira coupling with (trimethylsilyl)acetylene of compounds 16, which in turn can be prepared from compounds 15 by selective aminolysis at the chlorine atom.

Imidazopyrazines 15 can be readily synthesized from dichloropyrazine 11 by a minor modification of a literature procedure. (See *J. Med. Chem.* Vol. 26 (1983), at pp. 10 357-36.) For example, dichloropyrazine 11 upon treatment with 1-amino-2-propanol affords compounds 12; compounds 12 can be brominated with NBS to form compounds 13; compounds 13 can be converted to 14 upon treatment with DMSO/oxalyl chloride, followed by addition of TEA; and compounds 14 can be cyclized to imidazopyrazines 15 when treated with trifluoroacetic anhydride/trifluoroacetic acid.

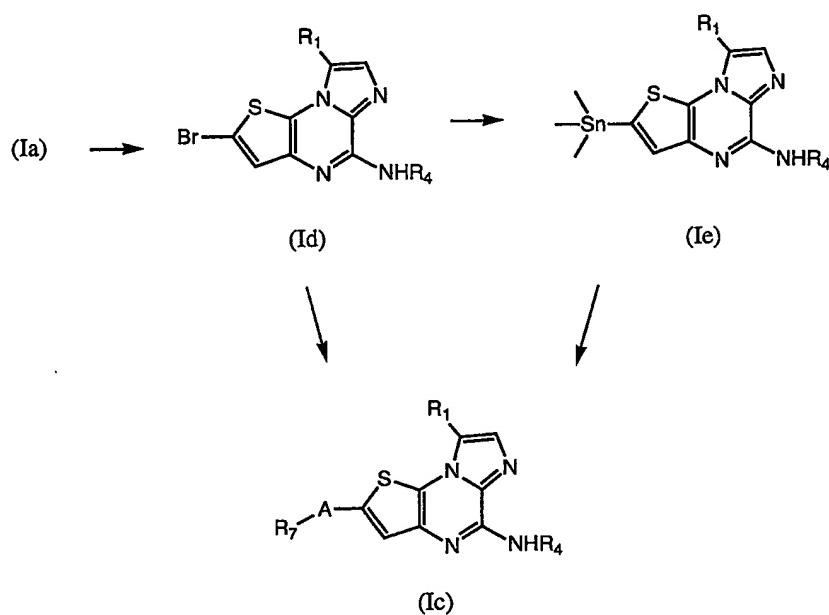
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Scheme IV

Substituted thienoimidazopyrazines (**Ic**) can be prepared from compounds **18** (Scheme III), via desilation to afford alkynes **19**. Coupling **19** with various aryl or heteroaryl halides provides substituted chloroalkynes **20** which can be cyclized to compounds of formula (**Ic**) by treatment with Na₂S·9H₂O in a solvent such as DMF. (See *J. Chem. Research*, (1985) at p. 1682).

Scheme V

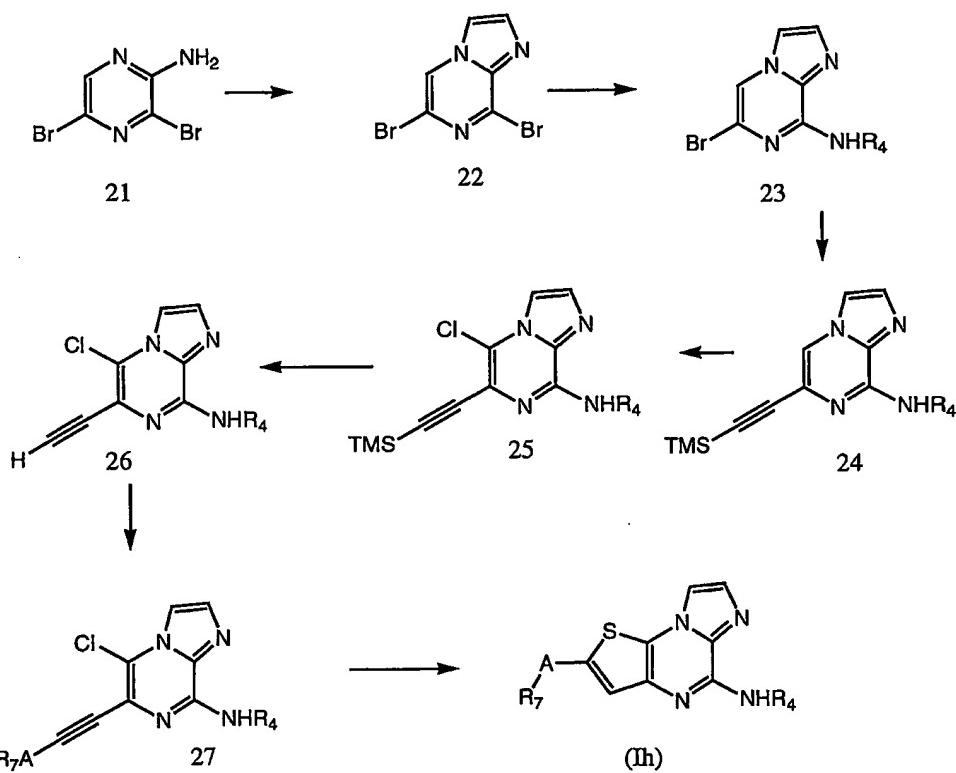
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Alternatively, various substituted thienoimidazopyrazines (**Ic**) can be prepared from compounds (**Ia**) upon bromination of (**Ia**) with NBS in chloroform to form compounds (**Id**). Compounds (**Id**) can be coupled with various aryl or heteroaryl stannanes and boronic acids to directly form compounds (**Ic**). Alternatively, bromides (**Id**) can be first stannylylated to compounds (**Ie**) and then compounds (**Ie**) may be coupled with various aryl or heteroaryl halides or triflates under Stille conditions to form

compounds of formula (Ic). If the molecule contains protected functional groups, then appropriate protocols are employed to remove the protection groups. For example, when NHR_4 comprises a Boc-protected amine, removal of the Boc group may be effected using TFA/ CH_2Cl_2 .

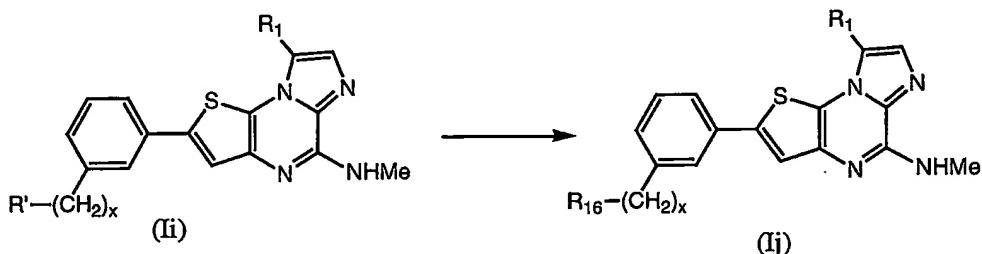
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Scheme VI

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Scheme VI shows methods similar to those in Schemes III and IV for making compounds of Formula (I) where $R_1 = \text{H}$, by starting from dibromide 22. Dibromide 22 was obtained from the condensation of chloroacetaldehyde and aminopyrazine 21 by employing a procedure described in Biorganic & Medicinal Chemistry, Vol. 7, (1999), at p. 1059.

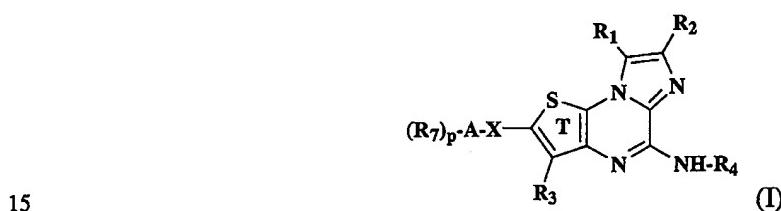
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Scheme VII

Compounds of formula (Ia) through (Ih) prepared as described in Schemes I through VI can be further elaborated into multiple final products applying techniques known in the field. As a non-limiting illustration, compounds of formula (Ii) containing R' can be further elaborated to form compounds of formula (Ij). For example, where R' is Br, compounds of (Ii) can be converted into compounds of (Ij) where R₁₆ is NR₁₇R₁₈ by aminolysis. Alternatively, where R' is COOR'', synthesis of (Ij) where R₁₆ is CONHR₁₇ can likewise be achieved via aminolysis. Compounds (Ii) can be prepared as described above in Schemes IV and V.

Preferred Compounds

Preferred compounds are compounds of formula (I),



and pharmaceutically-acceptable salt, hydrate or prodrug thereof, in which:

- R₁ is methyl;
- R₂ is hydrogen;
- 20 R₃ is hydrogen or lower alkyl;
- R₄ is -(CR₅R₆)_m-Z;

R_5 and R_6 at each occurrence are independently selected from hydrogen, alkyl, substituted alkyl, amino, alkylamino, substituted alkylamino, hydroxy, alkoxy, or substituted alkoxy;

R_7 at each occurrence is selected independently of each other R_7 from alkyl, substituted

- 5 alkyl, alkenyl, substituted alkenyl, halogen, cyano, $-(CR_{5a}R_{6a})_q-OR_{8a}$,
- $-(CR_{5a}R_{6a})_q-NR_8R_9$, $-(CR_{5a}R_{6a})_q-NR_{8a}SO_2(C_{1-4}\text{alkyl})$, $-(CR_{5a}R_{6a})_q-SO_2NR_8R_9$,
- $-(CR_{5a}R_{6a})_q-NR_{8a}C(=O)R_{9a}$, $-(CR_{5a}R_{6a})_q-NR_{8a}CO_2R_{9a}$, $-(CR_{5a}R_{6a})_q-C(=O)R_{8a}$,
- $-(CR_{5a}R_{6a})_q-CO_2R_{8a}$, $-(CR_{5a}R_{6a})_q-C(=O)NR_8R_9$, $-(CR_{5a}R_{6a})_q-OC(=O)NR_8R_9$, five or six membered optionally substituted heterocycle or heteroaryl, or

- 10 (heterocylo)alkyl, or when A is an unsaturated heterocycle, one of R_7 may be keto ($=O$), or when A is absent, R_7 may be hydrogen;

X is a bond, $-CH=CH-$, or $-C\equiv C-$;

A is a bond, phenyl, five or six membered heteroaryl;

Z is selected from hydrogen, methyl, hydroxy, $-NHC(=O)R_{13}$, $-NHCO_2R_{13}$, and

- 15 $-NR_{14}R_{15}$;

R_8 and R_9 are independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, heterocycle, aryl and heteroaryl;

R_{12} is hydrogen or lower alkyl;

R_{13} is alkyl, substituted alkyl, cycloalkyl, heterocyclo, aryl or heteroaryl;

- 20 R_{14} and R_{15} are independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, heterocycle, aryl and heteroaryl;

M and q are independently 0, 1, 2, 3, or 4; and

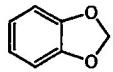
p is 0, 1, 2, or 3, except when A is absent, then p is 1.

- 25 More preferred are compounds of formula (I), as immediately defined above, wherein:

R_4 is $-(CH_2)_m-Z$;

Z is hydrogen, methyl, hydroxy, $-NH_2$, $-NH(C_{1-4}\text{alkyl})$, $-NHCO_2(C_{1-4}\text{alkyl})$, or $-N(C_{1-4}\text{alkyl})_2$; and

A is attached to X and thienyl ring T at any available carbon or nitrogen atom of A and is selected from phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl, pyrazolyl, thienyl, thiazolyl, furyl, pyrrolyl, pyranyl, dihydropyridyl, and

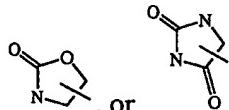


, wherein A has 0 to 3 substituents selected from R₇.

5

Those skilled in the field will recognize that R₇ groups when present as a substituent on ring "A" may be selected from those groups recited above as well as possible equivalents known in the field. However, preferably R₇ substituents are selected from the groups consisting of:

- 10 a) hydrogen, cyano, trifluoromethyl, halogen, hydroxy, -(CR_{5a}R_{6a})_q-O(C₁₋₄alkyl),
-(CR_{5a}R_{6a})_q-NH₂, -(CR_{5a}R_{6a})_q-NH(C₁₋₄alkyl),
-(CR_{5a}R_{6a})_q-NH(C₁₋₄aminoalkyl), -(CR_{5a}R_{6a})_q-NH(C₁₋₄hydroxyalkyl),
-(CR_{5a}R_{6a})_q-N(C₁₋₄alkyl)₂, -(CR_{5a}R_{6a})_q-NH(CH₂)_r(alkylamino),
-(CR_{5a}R_{6a})_q-NH(CH₂)_r(pyrrolidinyl), -(CR_{5a}R_{6a})_q-NHC(=O)H,
-(CR_{5a}R_{6a})_q-NHC(=O)C₁₋₄alkyl, -(CR_{5a}R_{6a})_q-C(=O)C₁₋₄alkyl,
15 -(CR_{5a}R_{6a})_q-C(=O)(CH₂)_r(morpholinyl), -(CR_{5a}R_{6a})_q-C(=O)(CH₂)_r(imidazolyl),
-(CR_{5a}R_{6a})_q-C(=O)(CH₂)_r(alkylamino), -(CR_{5a}R_{6a})_q-C(=O)NH₂,
-(CR_{5a}R_{6a})_q-CO₂H, -(CR_{5a}R_{6a})_q-CO₂(C₁₋₄alkyl), -(CR_{5a}R_{6a})_q-OC(=O)NH₂,
-(CR_{5a}R_{6a})_q-OC(=O)NH(C₁₋₄alkyl), and -(CR_{5a}R_{6a})_q-OC(=O)N(C₁₋₄alkyl)₂;
- 20 b) heterocycles or heteroaryls including morpholinyl, piperazinyl, pyrrolidinyl,

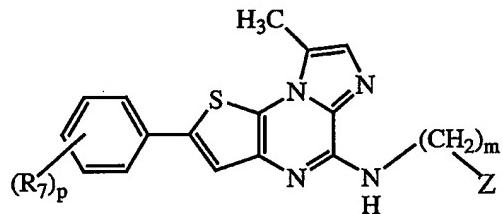


, or in turn optionally substituted with one to three C₁₋₄alkyl, hydroxyalkyl, amino, alkylamino, and/or keto; and

- c) C₁₋₆alkyl optionally substituted with one to two of hydroxy, cyano, halogen,
-NH₂, -NH(C₁₋₄alkyl), -NH(C₁₋₄aminoalkyl), -NH(C₁₋₄hydroxyalkyl),
-N(C₁₋₄alkyl)₂, -NH(C=O)H, -NH(C=O)C₁₋₄alkyl, -NHSO₂(C₁₋₄alkyl),
-C(=O)NH₂, -C(=O)(morpholinyl), -CO₂H, -CO₂(C₁₋₄alkyl), heterocycle,

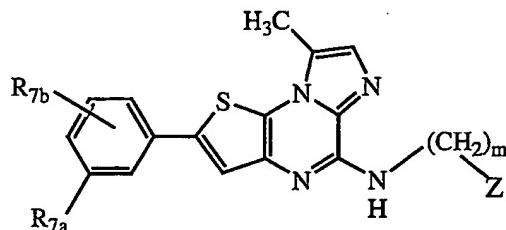
and/or heteroaryl said heterocycle or heteroaryl in turn optionally substituted with one to three C₁₋₄alkyl, hydroxyalkyl, amino, alkylamino, C(=O)H, C(=O)C₁₋₄alkyl, and/or keto.

5 Most preferred compounds include those having the formula:



- and pharmaceutically-acceptable salts, hydrates, or prodrugs thereof, in which:
- 10 Z is hydrogen, methyl, hydroxy, -NH₂, -NH(C₁₋₄alkyl), -NHCO₂(C₁₋₄alkyl) or -N(C₁₋₄alkyl)₂;
- R₇ is C₁₋₆alkyl optionally substituted with one to two of hydroxy, cyano, halogen, -NH₂, -NH(C₁₋₄alkyl), -NH(C₁₋₄aminoalkyl), -NH(C₁₋₄hydroxyalkyl), -N(C₁₋₄alkyl)₂, -NH(C=O)H, -NH(C=O)C₁₋₄alkyl, -NHSO₂(C₁₋₄alkyl), -C(=O)NH₂, -C(=O)(morpholinyl), -CO₂H, -CO₂(C₁₋₄alkyl), and/or a heterocycle or heteroaryl selected from morpholinyl, pyrazolyl, imidazolyl, piperazinyl, and pyrrolidinyl, said heterocycle or heteroaryl in turn optionally substituted with one to three C₁₋₄alkyl, hydroxyC₁₋₄alkyl, amino, C₁₋₄alkylamino, C(=O)H, C(=O)C₁₋₄alkyl, and/or keto;
- 15 m is 1, 2, 3 or 4;
- 20 q is 0 1, 2 , 3 or 4 and
- p is 1 or 2.

Most preferred compounds include compounds having the formula:



wherein

R_{7a} is

a) $-(\text{CR}_{5a}\text{R}_{6a})_q-\text{NR}_8\text{R}_9$, and

5 R_{5a} and R_{6a} at each occurrence are selected from hydrogen, methyl,
 hydroxy, amino or alkylamino;
 R_8 is hydrogen or alkyl;
 R_9 is alkyl substituted with $-\text{C}(=\text{O})\text{NH}_2$ or $-\text{C}(=\text{O})\text{NH}(\text{alkyl})$;
 q is 0, 1 or 2 (especially 1 or 2)

b) $-(\text{CR}_{5a}\text{R}_{6a})_q-\text{CO}_2\text{R}_{8a}$

10 R_{5a} and R_{6a} at each occurrence are selected from hydrogen, methyl,
 hydroxy, amino or alkylamino;
 R_{8a} is alkyl;
 q is 0, 1 or 2 (especially 1 or 2)

c) $-(\text{CR}_{5a}\text{R}_{6a})_q-\text{C}(=\text{O})\text{NR}_8\text{R}_9$

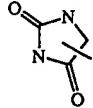
15 R_{5a} and R_{6a} at each occurrence are selected from hydrogen, methyl,
 hydroxy, amino or alkylamino;

R_8 is hydrogen;

R_9 is alkyl;

20 q is 0, 1 or 2 (especially 1 or 2)

d) heterocyclo or (heterocyclo)alkyl especially where heterocyclo is



R_{7b} is absent or halo (especially fluorine).

Utility

The compounds and compositions of this invention are useful in treating conditions that are characterized by the activity of IKK, release of NF- κ B, and/or enhanced levels of TNF- α . The term “treating” or “treatment” denotes prevention, 5 partial alleviation, or cure of the disease or disorder or its symptoms or consequences. Inhibition or suppression of IKK, NF- κ B and/or TNF- α may occur locally, for example, within certain tissues of the subject, or more extensively throughout the subject being treated for such a disease. Inhibition or suppression of IKK, NF- κ B and/or TNF- α may occur by one or more mechanisms, *e.g.*, by inhibiting or suppressing any step of the 10 pathway(s). The term “NF- κ B-associated condition” refers to diseases that are characterized by release of NF- κ B from the cytoplasm (*e.g.*, upon phosphorylation of I κ B). The term “TNF- α -associated condition” is a condition characterized by enhanced 15 levels of TNF- α . In the instant specification, the term “NF- κ B-associated condition” will include a TNF- α -associated condition but is not limited thereto as NF- κ B is involved in the activity and upregulation of other pro-inflammatory proteins and genes. The term “inflammatory or immune disease” is used herein to encompass IKK-associated 20 conditions, NF- κ B-associated conditions, and TNF- α -associated conditions, *e.g.*, any condition, disease, or disorder that is associated with activity of IKK, NF- κ B and/or enhanced levels of TNF- α .

20 The inventive compounds and compositions are useful for treating a variety of diseases including, but not limited to, treatment of transplant rejections (*e.g.*, kidney, liver, heart, lung, pancreas, bone marrow, cornea, small bowel, skin allografts, skin homografts and heterografts, etc.); rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, inflammatory bowel disease (such as Crohn’s disease and ulcerative colitis); 25 antiviral and autoimmune diseases including herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), cytomegalovirus, Epstein-Barr, human immunodeficiency virus (HIV), Addison’s disease (autoimmune disease of the adrenal glands), idiopathic adrenal insufficiency, and autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome); Alzheimer’s, Parkinson’s, and Creutzfeldt-Jacob diseases;

septic shock; hematopoiesis; inflammatory diseases such as osteoarthritis, acute pancreatitis, and chronic pancreatitis; inflammatory disorders of the central nervous system, including HIV encephalitis, cerebral malaria, and meningitis, atherosclerosis, and ataxia telangiectasis; respiratory allergies including asthma, hayfever, and allergic rhinitis; fungal infections such as mycosis fungoides; and psoriasis, glomerulonephritis, serum sickness, lupus (systemic lupus erythematosus), urticaria, scleroderma, contact dermatitis, dermatomyositis, alopecia, atopic eczemas, and ichthyosis. The term "inflammatory or immune disease" as used herein includes all of the above-referenced diseases and disorders.

10 The inventive compounds are also effective in treating oncological diseases, in treating cancer and tumors, such as solid tumors, lymphomas and leukemia, and in particular, breast cancer, prostate cancer, and Hodgkin's lymphoma.

15 The present invention thus provides methods for treating such conditions, comprising administering to a subject in need thereof an effective amount of at least one compound of formula I or a salt thereof. Other therapeutic agents such as those described below may be employed in combination with compounds of formula I. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following administration of the inventive compound(s).

20 The present invention also provides pharmaceutical compositions capable of treating IKK, NF- κ B and/or TNF- α associated conditions, as described above. The inventive compositions may contain other therapeutic agents and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to 25 techniques such as those well known in the art of pharmaceutical formulation.

25 The compounds of formula I may be administered by any means suitable for the condition to be treated, which may depend on the need for site-specific treatment or quantity of drug to be delivered. Topical administration is generally preferred for skin-related diseases, and systematic treatment preferred for cancerous or pre-cancerous 30 conditions, although other modes of delivery are contemplated. For example, the

compounds may be delivered orally, such as in the form of tablets, capsules, granules, powders, or liquid formulations including syrups; topically, such as in the form of solutions, suspensions, gels or ointments; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular or intrasternal injection or infusion techniques
5 (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; rectally such as in the form of suppositories; or liposomally. Dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents may be administered. The compounds may be administered in a form suitable for immediate release or extended
10 release. Immediate release or extended release may be achieved with suitable pharmaceutical compositions or, particularly in the case of extended release, with devices such as subcutaneous implants or osmotic pumps.

Exemplary compositions for topical administration include a topical carrier such as PLASTIBASE® (mineral oil gelled with polyethylene).

15 Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate,
20 starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The inventive compounds may also be orally delivered by sublingual and/or buccal administration, e.g., with molded, compressed, or freeze-dried tablets. Exemplary compositions may include fast-dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also
25 included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl cellulose (SCMC), and/or maleic anhydride copolymer (e.g., GANTREZ®); and agents to control release such as polyacrylic copolymer (e.g.,

CARBOFOL 934®). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, 5 absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's 10 solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, 15 synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a mammal of from about 0.05 to 100 mg/kg of body weight of active compound per day, which may 20 be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and 25 diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats, horses, and the like, subject to IKK, NF-κB and/or TNF- α associated conditions.

The inventive compounds and compositions may be employed alone or in combination with each other and/or other suitable therapeutic agents useful in treating IKK, NF- κ B and/or TNF- α associated conditions. Exemplary of such other therapeutic agents include corticosteroids, rolipram, calphostin, CSAIDs, 4-substituted imidazo [1,2-5 A]quinoxalines as disclosed in US Pat. No. 4,200,750; Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; nuclear translocation inhibitors, such as deoxyspergualin (DSG); non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and rofecoxib; steroids such as prednisone or dexamethasone; antiviral agents such as abacavir; antiproliferative agents such as methotrexate, 10 leflunomide, FK506 (tacrolimus, Prograf); cytotoxic drugs such as azathiprine and cyclophosphamide; TNF- α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof; and other cancer drugs and treatments, including radiation treatments and daunorubicin.

15 The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

The inventive compounds have been tested and have shown activity as inhibitors of IKK, IkB, NF- κ B and/or TNF- α . For example, THP-1 (human monocytic cell line) 20 obtained from ATCC was cultured in RPMI-1640 supplemented with 10 % FBS, sodium pyruvate, HEPES, 5-mercaptoproethanol, Penicillin/Streptomycin. To a 96-well plate containing THP-1 cells (1.4×10^6 /mL, 2.5×10^5 cells/well) in 180 μ L RPMI-1640 was added 10 μ L of the test compound in 10 % DMSO. Typically, test compound 25 concentrations of 0.1-100 μ M were used in the assay. After one hour at 37°C, 10 μ L of 1000 ng/mL lipopolysaccharide (LPS from *Salmonella typhosa*, Sigma) was added to each well. After an additional 6 hours at 37°C, the supernatants were collected following a 5 minute centrifugation of the plate to pellet the cells. The amount of TNF α in these supernatants was then measured using a TNF α -specific ELISA (Pharmingen). After subtracting out the amount of TNF α in a control that had not been treated with LPS, the

percent inhibition was calculated versus a control that was treated with LPS but with no test compound added. The compounds of this invention are active *in vivo* in the LPS-induced TNF α secretion model. Likewise, assays known in the field are applied to establish the activity of the compounds as inhibitors of IKK, I κ B, and/or the NF- κ B pathway.

Abbreviations

For ease of reference, the following abbreviations are employed herein, including in the methods of preparation hereinbefore and in the Examples that follow:

- 10 Ph = phenyl
Bz = benzyl
t-Bu = tertiary butyl
Me = methyl
Et = ethyl
15 Pr = propyl
Iso-P = isopropyl
MeOH = methanol
EtOH = ethanol
EtOAc = ethyl acetate
20 Boc = tert-butyloxycarbonyl
CBZ = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl
DMF = dimethyl formamide
DMSO = dimethyl sulfoxide
TEA = triethylamine
25 TFA = trifluoroacetic acid
THF = tetrahydrofuran
KOH = potassium hydroxide
K₂CO₃ = potassium carbonate
POCl₃ = phosphorous oxychloride

- KOtBu = potassium t-butoxide
HOBt = 1-hydroxybenzotriazole hydrate
NaH = sodium hydride
NaOH = sodium hydroxide
5 Na₂S₂O₃ = sodium thiosulfate
Pd = palladium
min. = minute(s)
L = liter
mL = milliliter
10 µL = microliter
g = gram(s)
mg = milligram(s)
mol = moles
mmol = millimole(s)
15 meq = milliequivalent
RT = room temperature
ret. t. = HPLC retention time (minutes)
sat or sat'd = saturated
aq. = aqueous
20 TLC = thin layer chromatography
HPLC = high performance liquid chromatography
LC/MS = high performance liquid chromatography/mass spectrometry
MS = mass spectrometry
NMR = nuclear magnetic resonance
25 mp = melting point

The following Examples illustrate embodiments of the invention and are not intended to limit the scope of the claims. In the following Examples, anhydrous reactions were performed under an atmosphere of nitrogen or argon using either commercially available dry solvents or freshly distilled solvents. Column chromatography was

performed using EM Science silica gel 60 with the designated solvent system as eluant. HPLC purification was conducted using a Shimadzu LC8A with YMC S5 ODS or xTerra MS C₁₈ columns. HPLC purity determinations were done using either an HP 1090 DRS with a diode array detector and a Waters Nova-Pak C₁₈ column, or a Shimadzu LC-10AS 5 with a SPD-10AV UV-V detector and Waters xTerra C₁₈ column. Melting points were determined in an open capillary tube with a Thomas-Hoover melting point apparatus.

¹H-NMR spectra were recorded in DMSO (δ = 2.50 ppm) using a 500 MHZ instrument (unless otherwise stated) and chemical shifts are expressed in parts per million (ppm or δ) with the solvent in use as an internal standard. Coupling constants are given in 10 Hertz, and multiplets are designated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), and apparent (app).

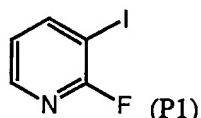
Low resolution mass spectra were determined with a Finnigan Matt TSQ-7000 or SSQ-700, or with a Shimadzu LC-10AS coupled with Waters Micromass ZQ. HRMS were determined with a Finnigan Matt 900.

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Examples for Preparation of Intermediate
Halide-Coupling Components (R₇-A-Br and R₇-A-I)

Preparation 1

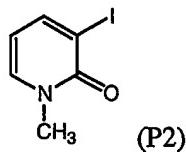
20



2-Fluoro-3-iodopyridine (P1) was prepared from 2-fluoropyridine according to the procedure in Heterocycles, Vol. 35 (#1) (1993), at p. 151.

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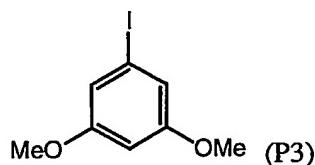
Preparation 2



A mixture of 2-fluoro-3-iodopyridine (1.035 g, 4.6415 mmol) and iodomethane (3.0 mL, 48.190 mmol) in a pressure tube was heated at 70°C for 20.5 h. The reaction
 5 mixture was allowed to cool to rt, and the white suspension was filtered and washed with EtOAc and exposed to vacuum to afford the *N*-methyl pyridinium salt (284.1 mg). This salt was treated with NaOH solution (3.0 mL, 1.0 M/H₂O) and stirred at rt for 30 min.
 and at 70°C for 30 min. The reaction mixture was cooled to rt, diluted with brine and extracted with EtOAc. The organic layer was dried (MgSO₄), filtered, and evaporated *in*
 10 *vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (EtOAc) to afford pyridone P2 as a yellow oil (165 mg, 15.1 %). ¹H NMR: 8.08 (dd, J = 7.3, 1.8, 1H), 7.77 (dd, J = 6.6, 2.1, 1H), 6.03 (app t, J = 6.9, 1H), 3.48 (s, 3H). (ESI) m/z (M+H)⁺ = 236.08.

15

Preparation 3

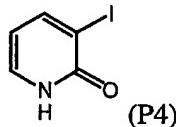


20 Water (15.0 mL), concentrated HCl (10 mL, ~37 %) and 3,5-dimethoxyaniline (4.3725 g, 28.5775 mmol) were mixed sequentially and the heterogeneous mixture was stirred for 50 min. The mixture was then cooled to 0°C and treated with an aqueous solution of NaNO₂ (2.6164 g/11 mL, 37.91 mmol) over 7 min. After the reaction mixture was stirred for 15 min, it was slowly added to a beaker containing a cooled (0°C) aqueous
 25 (10.0 mL) solution of KI (10.01 g, 60.30 mmol) over 10 min. The cooling bath was

removed 13 min. later and the reaction mixture was allowed to thaw to rt over 1 hr. It was then heated to 95°C for about 30 min, and during this heating the side of the beaker was washed with water (10 mL). The mixture was allowed to cool to rt and extracted with ether. The organic phase was washed with water, a solution of NaOH/Na₂SO₃ (5 g 5 of Na₂SO₃ dissolved in 50 mL of 1.0 M NaOH/H₂O) and brine. It was dried (MgSO₄), filtered and evaporated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (5 % EtOAc/hexanes) to afford iodide P3 as a white solid (3.979 g, 52.6 %). ¹H NMR (CDCl₃, δ = 7.26 ppm; 500 MHZ): 6.86 (d, J = 2.4, 2H), 6.40 (t, J = 2.3, 1H), 3.76 (s, 6H).

10

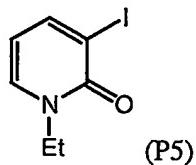
Preparation 4



15 NaOH (8.0 mL, 1.0 N/H₂O) was added to a THF (10.0 mL) solution of the fluoropyridine P1 (1.6281 g, 7.30 mmol), and the biphasic mixture was stirred at 80°C for 91.5 h; during this time most of the THF evaporated. The reaction mixture was cooled to rt and the remaining solvent was removed *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (0-20 % 20 EtOAc/hexanes) to afford pyridone P4 as an off-white solid (504.4 mg, 31.3 %). ¹H NMR: 11.94 (br s, 1H), 8.10 (dd, J = 7.0, 1.8, 1H), 7.45 (dd, J = 6.5, 1.9, 1H), 5.99 (app t, J = 6.8, 1H). (ESI) m/z (M+H)⁺ = 221.97.

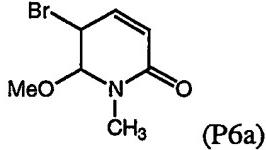
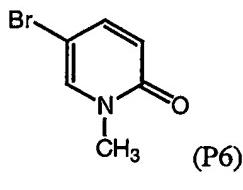
Preparation 5

25



Potassium *tert*-butoxide (1.3 mL, 1.0 M/THF) and ethyliodide (300 μ L, 3.751 mmol) were added to a THF (3.0 mL) solution of pyridone P4 (256.7 mg, 1.1619 mmol).
 5 The resulting clear solution was stirred at rt for 21.5 h. The reaction mixture was diluted with sat'd NH₄Cl solution and extracted with EtOAc (2x). The organic layer was washed with brine, dried ($MgSO_4$), filtered and evaporated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (60 % EtOAc/hexanes) to afford pyridone P5 as a yellow oil (268.4 mg, 92.8 %). ¹H NMR: 8.08 (dd, J = 7.0, 1.9, 1H), 7.78 (dd, J = 6.8, 1.9, 1H), 6.05 (app t, J = 6.9, 1H), 3.95 (q, J = 7.1, 2H), 1.21 (t, J = 7.0, 3H). (ESI) m/z (M+H)⁺ = 249.94
 10

Preparation 6



15

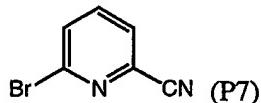
N-Bromosuccinimide (1.7976 g, 16.472 mmol) was added to a MeOH (15.0 mL) solution of commercially-available N-methyl-2-pyridone (1.02 g, 9.347 mmol). The reaction flask was covered with aluminum foil and stirred at rt for 18 h. The solvent was removed *in vacuo*, and a silica gel mesh of the crude material was prepared and submitted to flash chromatography (30–70 % EtOAc/hexanes) to retrieve the major component P6a as a colorless oil (965.4 mg). A fraction was also retrieved that contained bromide P6 and

its C₃-Br regioisomer in ~4.1/5.3 mole ratio (647.4 mg, colorless oil). ¹H NMR of P6a: 6.78 (ddd, J = 9.5, 5.7, 1.7, 1H), 5.93 (d, J = 9.4, 1H), 5.10 (dd, J = 5.5, 1.6, 1H), 4.97 (app t, J = 1.5, 1H), 3.37 (s, 3H), 3.01 (s, 3H). (ESI) m/z (M+H)⁺ = 220.07/222.07.

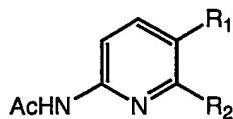
NaN(TMS)₂ (3.0 mL, 1.0 M/THF) was added dropwise to a THF (10.0 mL) solution of bromide P6a (960 mg, 4.3624 mmol) over 1 hr. Each drop caused the appearance of a brown suspension that disappeared slowly. The reaction mixture was stirred for an additional 30 min. and quenched with sat'd NH₄Cl solution (0.5 mL). The organic layer was separated and evaporated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (EtOAc) to afford bromide P6 as a faint yellow solid (651 mg, a two step combined yield of 37 %). ¹H NMR: 8.03 (d, J = 2.8, 1H), 7.52 (dd, J = 9.6, 2.9, 1H), 6.34 (d, J = 9.4, 1H), 3.40 (s, 3H). (ESI) m/z (M+H)⁺ = 188.02/190.02.

Preparation 7

15



DMF (10 mL) was added into a mixture of commercially-available 2,6-dibromopyridine (1.0470 g, 4.4194 mmol) and CuCN (402 mg, 4.4886 mmol). The reaction mixture was refluxed for 23 h. It was then cooled to rt, diluted with EtOAc and the suspension was filtered. The volatile component of the filtrate was removed *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (10-15 % EtOAc/hexanes) to afford bromopyridine P7 as a white solid (126.5 mg, 15.6 %). ¹H NMR (CDCl₃, δ = 7.26 ppm; 500 MHZ): 7.74 (dd, J = 7.7, 1.9, 1H), 7.71 (app t, J = 7.3, 1H), 7.68 (dd, J = 7.0, 2.1, 1H). (ESI) m/z (M+H)⁺ = 183.04/185.04.

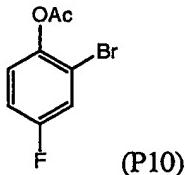
Preparations 8 and 9

P8: R₁ = Br, R₂ = H

P9: R₁ = H, R₂ = Br

- 5 Triethylamine (0.650 mL, 4.6635 mmol) and acetic anhydride (1.30 mL, 13.7780 mmol) were added into a THF (6.0 mL) solution of the appropriately-substituted aminopyridine (507.9 mg, 2.94 mmol). The reaction mixture was stirred at 65°C for 20 h, cooled to rt, and the volatile component removed *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (10-15 % EtOAc/hexanes) to afford the acylated pyridine compounds P8 and P9 as white solids.
- 10 For P8: 94.4 % yield. ¹H NMR: 10.64 (br s, 1H), 8.41 (dd, J = 2.5, 0.6, 1H), 8.06 (d, J = 8.9, 1H), 7.98 (dd, J = 8.9, 2.5, 1H), 2.09 (s, 3H). For P9: 89.6 % yield. ¹H NMR: 10.79 (br s, 1H), 8.08 (app d, J = 8.0, 1H), 7.71 (app t, J = 8.0, 1H), 7.31 (app d, J = 7.9, 1H), 2.08 (s, 3H). (ESI) m/z (M+H)⁺ = 215.01/217.01.

15

Preparation 10

- 20 A THF (5.0 mL) solution of 2-bromo-4-fluorophenol (200 mg, 1.05 mmol) was treated with TEA (300 uL, 2.152 mmol), acetic anhydride (200 uL, 2.1 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred overnight at rt, diluted with EtOAc, and washed with 1 N HCl, sat'd aqueous NaHCO₃ solution and brine. It was

then dried (MgSO_4), filtered and evaporated *in vacuo*. Acylated phenol P10 was retrieved as a colorless oil (215.6 mg, 82 %).

Preparations 11 and 12

5

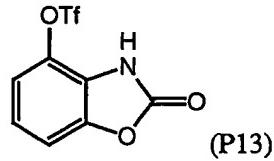


NaN(TMS)₂ (4.50 mL, 1.0 M/THF) was added to a THF (5.0 mL) solution of 2-amino-5-bromopyridine (0.5007 g, 2.8939 mmol) and stirred at rt for 10 min.

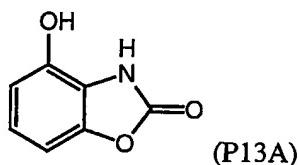
Iodomethane (400 uL, 6.4252 mmol) was added dropwise to the above solution over a few minutes. The reaction mixture was stirred at rt for 5.5 h, diluted with EtOAc, and washed with water and brine. The organic layer was dried (MgSO_4), filtered, and evaporated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (20 % EtOAc/hexanes) to afford pyridine P11 (light-pink solid, 127.8 mg, 23.6 %) and pyridine P12 (light yellow solid, 297 mg, 51.0 %). ¹H NMR of P11: 8.03 (d, J = 2.4, 1H), 7.50 (dd, J = 8.9, 2.5, 1H), 6.72 (br m, 1H), 6.43 (dd, J = 8.9, 0.7, 1H), 2.73 (d, J = 4.9, 3H). ¹H NMR of P12: 8.12 (dd, J = 2.5, 0.6, 1H), 7.63 (dd, J = 9.2, 2.8m, 1H), 6.61 (dd, J = 9.2, 0.6, 1H), 2.99 (s, 6H).

20

Preparation 13



25 Step A:

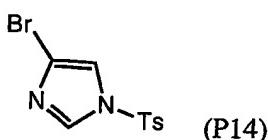


Phenol P13A was prepared from 2-nitroresorcinol according to EP 701907-A1.

5 Step B:

DMAP (672.6 mg, 5.51 mmol) and trifluoromethanesulfonic anhydride (780 uL, 1.15 mmol) were added into a cooled (0°C) CH₂Cl₂ (5.0 mL) solution of phenol P13A (585 mg, 3.87 mmol). The reaction mixture was stirred for 30 min, the bath was removed, and stirring continued for an additional 30 min. The reaction mixture was 10 poured into 1 N HCl and extracted with CH₂Cl₂. The organic layer was washed with brine, dried (MgSO₄), filtered and evaporated *in vacuo*. A silica gel mesh was prepared from the crude material and submitted to flash chromatography (50-100 % CH₂Cl₂/hexanes -> 20-50 % EtOAc/CH₂Cl₂) to afford triflate P13 as a light brown solid (640 mg, 58.1 %). ¹H NMR (MeOH-d4, δ= 3.30 ppm; 300 MHZ): 7.35-7.28 (m, 1H), 15 7.25-7.20 (m, 2H). (ESI) m/z (M+H)⁺ = 284.21.

Preparation 14

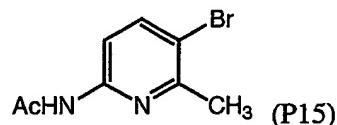


20

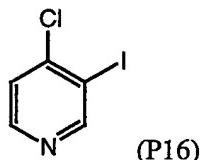
Compound P14 was prepared upon tosylation of 4-Bromoimidazole according to the literature procedure described in J. Org. Chem., Vol. 60 (1995), at pp. 2378-2383.

¹H NMR: 8.40 (d, J = 1.5, 1H), 8.05 (d, J = 1.5, 1H), 8.01 (m, 2H), 7.54 (d, J = 7.9 , 2H), 2.42 (s, 3H). (ESI) m/z (M+H)⁺ = 300.97/302.97.

25

Preparation 15

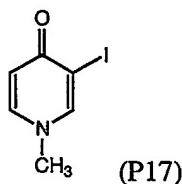
5 Pyridine P15 was prepared from 6-amino-3-bromo-2-methylpyridine according to the procedure described above for making compounds P8 and P9.

Preparation 16

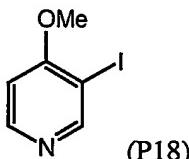
10

Butyllithium (33.0 mL, 1.6 M/hexanes) was added to a cooled (-78°C) THF (35 mL) solution of diisopropylamine (7.5 mL, 53.51 mmol) and stirred for 45 min. 4-chloropyridine (HCl salt, 3.8763 g, 25.84 mmol) was added in batches over 7 min. and the turbid yellow reaction mixture was stirred vigorously for 2 h. THF (15.0 mL) solution of I₂ (6.7560 g, 26.6194 mmol) was added dropwise over 13 min. while shaking manually. After completing the I₂ addition, the reaction mixture assumed a pasty texture and a spatula was used to mix it under a nitrogen atmosphere. The cooling bath was removed 70 min. later, and the reaction mixture was allowed to thaw over the next hour. It was quenched with 10 % Na₂S₂O₃ (50 mL), and extracted with EtOAc (50 mL, 2x). The organic layer was washed with brine, dried (MgSO₄), filtered and evaporated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (5-7 % EtOAc/hexanes) to afford iodide P16 as a white solid (2.772 g, 44.8 %). ¹H NMR: 8.98 (s, 1H), 8.50 (d, J = 5.2, 1H), 7.71 (d, J = 5.2, 1H). (ESI) m/z (M+H)⁺ = 239.89.

25

Preparation 17

5 A mixture of 4-chloro-3-iodopyridine (P16) (492.9 mg, 2.0586 mmol) and iodomethane (5.0 mL, 80.31 mmol) was heated at 70°C in a pressure tube for 50 h. The reaction mixture was cooled to rt and the precipitate was filtered, washed with EtOAc and dried *in vacuo*. The N-methyl pyridinium salt was obtained as an off-white solid (786.9 mg). NaOH solution (5 mL, 1M/H₂O) was added to this salt and the resulting
10 heterogeneous mixture was heated at 70°C for about 2 h. The reaction mixture was cooled to rt and the volatile component removed *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (0-20 % MeOH/EtOAc) to afford pyridone P17 as a yellow foam (473.5 mg, 97.7 %). ¹H NMR: 8.29 (d, J = 2.1, 1H), 7.68 (dd, J = 7.5, 2.3, 1H), 6.12 (d, J = 7.4, 1H), 3.64 (s, 3H). (ESI) m/z (M+H)⁺ = 15 235.95.

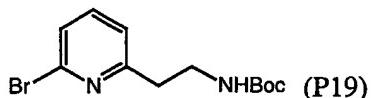
Preparation 18

20 A fresh sodium methoxide solution was prepared from sodium (222 mg, 9.6564 mmol) and MeOH (10 mL). 4-Chloro-3-iodopyridine (P16) (1.2071g, 5.023 mmol) was added in one batch and the reaction mixture was stirred at 75°C for 6 h. The solvent was removed *in vacuo* and a silica gel mesh was prepared from the crude material and submitted to flash chromatography (50 % EtOAc/hexanes) to afford methoxypyridine

P18 as a white crystalline solid (1.0166 g, 85.8 %). ^1H NMR: 8.69 (s, 1H), 8.39 (d, J = 5.5, 1H), 7.09 (d, J = 5.5, 1H), 3.91 (s, 3H). (ESI) m/z (M+H) $^+$ = 235.96.

Preparation 19

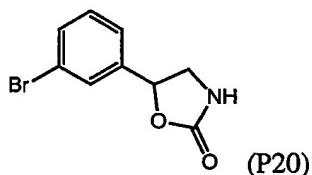
5



BH₃.Me₂S (2.60 mL of 2.0 M/THF) was added to a THF (3.0 mL) solution of (6-Bromo-pyridin-2-yl)acetonitrile (prepared according to Synlett, Vol. 10 [2000], at p. 1488) (505.6 mg, 2.5661 mmol). The mixture was stirred at rt for 20 min. and heated to 10 70°C for 4.5 h. It was cooled to rt, quenched with MeOH, and the volatile component was removed *in vacuo* to afford a crude product. Boc₂O (644.5 mg, 2.95 mmol) and DMAP (9.9 mg, 0.08 mmol) were added to a THF (7.0 mL) suspension of the above 15 crude product and the heterogeneous mixture was vigorously stirred at rt for 75 min. The solvent was removed *in vacuo*, and a silica gel mesh of the crude material was prepared and submitted to flash chromatography (20-30 % EtOAc/hexanes) to afford pyridine P19 as a faint yellow oil (225.9 mg, a combined yield of 29.2 %). ^1H NMR: 7.66 (app t, J = 7.6, 1H), 7.47 (d, J = 7.9, 1H), 7.29 (d, J = 7.6, 1H), 6.89 (br t, J = 5.4, 1H), 3.24 (app q, J = 6.7, 2H), 2.81 (t, J = 7.2, 2H), 1.36 (s, 9H). (ESI) m/z (M+H) $^+$ = 301.1/303.1.

20

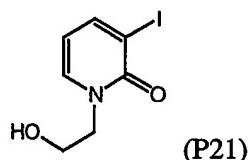
Preparation 20



25 1,1'-Carbonyldiimidazole (700.2 mg, 4.3182 mmol) was added to a THF (10 mL) semi-suspension of 2-amino-1-(3-bromo-phenyl)-ethanol (prepared according to J. Med.

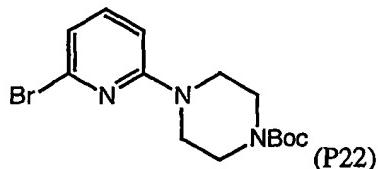
Chem., Vol. 14 [1971], at p. 266) (834 mg, 3.8597 mmol). The reaction mixture was stirred at rt for 15.5 h and at 70°C for 13.5 h. The reaction mixture was cooled to rt and the volatile component removed *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (60-70 % EtOAc/hexanes) to afford 5 oxazolidinone P20 along with a minor impurity as a white solid (563.7 mg). ¹H NMR (CDCl₃, δ = 7.26 ppm; 500 MHZ): 7.54 (m, 1H), 7.51 (m, 1H), 7.32-7.27 (m, 2H), 5.60 (app t, J = 8.0, 1H). 5.23 (br s, 1H), 4.00 (app t, J = 8.6, 1H), 3.51 (app t, J = 8.0, 1H). (ESI) m/z (M+H)⁺ = 242.08/244.08.

10

Preparation 21

K₂CO₃ (221 mg, 1.599 mmol) and bromoethanol (250 uL, 3.527 mmol) were 15 added into an acetone (4.0 mL) solution of compound P4 (244 mg, 1.1 mmol). The reaction mixture was heated at 65°C for 8 h and allowed to cool to rt. Silica gel was added to the reaction mixture and solvent removed *in vacuo*. The resulting mesh was submitted to flash chromatography (EtOAc) to afford alcohol P21 as a viscous oil (219.4 mg, 75.0 %). ¹H NMR: 8.08 (dd, J = 7.4, 1.9, 1H), 7.66 (dd, J = 6.7, 1.9, 1H), 6.02 (app t, 20 J = 6.9, 1H), 4.88 (br, s, 1H), 3.98 (t, J = 5.4, 2H), 3.61 (m, 2H). (ESI) m/z (M+H)⁺ = 265.98.

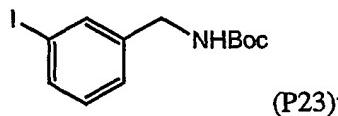
Preparation 22



Acetonitrile (10.0 mL) was added into a mixture of 2,6-dibromopyridine (1.0236 g, 4.3201 mmol), *N*-Boc piperazine (1.5548 g, 8.3475 mmol) and K₂CO₃ (1.0666 g, 7.7172 mmol). The reaction mixture was refluxed for ~ 64 h and allowed to cool to rt. It was diluted with EtOAc, filtered, and the filtrate was concentrated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (10 % EtOAc/hexanes) to afford bromide P22 as a white solid (1.2496 g, 84.5 %). ¹H NMR: 7.45 (dd, J = 8.3, 7.7, 1H), 6.81 (overlapping doublets, 2H), 3.47 (m, 4H), 3.41 (m, 4H), 1.42 (s, 9H). (ESI) m/z (M+H)⁺ = 342.14/344.14.

The synthesis of analogous amine-addition products was conducted under neat conditions where the dibromide was heated with an excess amount of amine (*e.g.* *tert*-butyl *N*-(2-aminoethyl)carbamate or ethanolamine) at 110°C until completion of the reaction. The reaction mixture was then cooled to rt and submitted to standard flash chromatography to afford the mono-adducts in >85 % yield.

Preparation 23

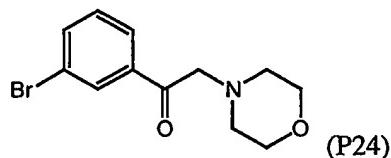


TEA (520 uL, 3.71 mmol), di-*tert*-butyldicarbonate (0.81 g, 3.71 mmol) and DMAP (0.45 g, 3.71 mmol) were sequentially added to a THF (20 mL) solution of 3-iodobenzylamine hydrochloride (1.00 g, 3.71 mmol), and the reaction mixture was heated at 50°C for 15 h. After it was allowed to cool to rt, the volatile component was removed *in vacuo*, and the residue dissolved in EtOAc and washed with water and brine.

The organic layer was dried (MgSO_4), filtered, and evaporated *in vacuo* to afford a mixture of iodide P23 and DMAP (1.3:1.0 mole ratio) as a white semi-solid (1.60 g). The mixture was used for coupling without further purification.

5

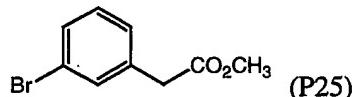
Preparation 24



K_2CO_3 (246.3 mg, 1.7821 mmol) and morpholine (400 μL , 4.5868 mmol) were added into a THF (5.0 mL) solution of 2,3'-dibromoacetophenone (512.4 mg, 1.84 mmol) and stirred at rt. A heavy suspension formed immediately after the morpholine was added and the reaction mixture was stirred overnight. Silica gel was added into the mixture and the solvent was removed *in vacuo*. The resulting silica gel mesh was submitted to flash chromatography (40 % EtOAc/hexanes) to isolate bromide P24 as a colorless crystal (468.5 mg, 89.4 %). ^1H NMR (CDCl_3 , δ = 7.26 ppm; 500 MHZ): 8.14 (app t, J = 1.7, 1H), 7.94 (m, 1H), 7.71 (m, 1H), 7.35 (app t, J = 8.0, 1H), 3.77 (m, 6H), 2.60 (m, 4H). (ESI) m/z $(\text{M}+\text{H})^+$ = 284.16/286.16.

20

Preparation 25

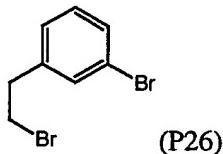


TMSCHN₂ (10.0 mL of 2.0 M/hexanes) was added dropwise over 35 min. to a toluene/MeOH (20/8 mL) solution of 3-bromophenylacetic acid (2.01 gms, 9.34 mmol). The reaction mixture was stirred for 45 min. and quenched with acetic acid. The volatile component was removed *in vacuo* to afford ester P25 as a yellow oil (2.08 g, 97.2 %). ^1H

NMR (CDCl_3 , $\delta = 7.26 \text{ ppm}$; 500 MHZ): 7.44 (m, 1H), 7.41 (app dt, $J = 7.0, 2.0, 1\text{H}$), 7.23-7.18 (m, 2H), 3.71 (s, 3H), 3.60 (s, 2H). (ESI) m/z ($M+\text{H}^+$)⁺ = 229.0/231.0.

Preparation 26

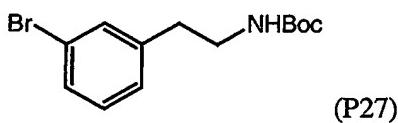
5



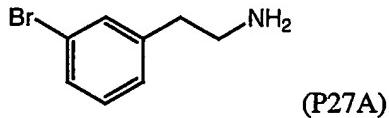
Ph₃P-Br₂ (4.90 g, 11.608 mmol) was added in batches over a few min. to a CH₃CN (30.0 mL) solution of 3-bromophenylethanol (2.0055 g, 9.9741 mmol), and the reaction mixture was stirred at rt for 19.25 h. The volatile component was removed *in vacuo*, and the residue was diluted with hexanes/ether (1:1, 50 mL), shaken briefly, and filtered. The filtered solid was washed with hexanes/ether (1:1, 50 mL). The combined filtrate was rotovaped to afford a colorless oil. ¹H NMR analysis of the oil indicated that the desired dibromide P26 contained a Ph₃PO impurity in a ~ 30:1 mole ratio (1.7585 g, ~64 %). ¹H NMR (CDCl_3 , $\delta = 7.26 \text{ ppm}$; 500 MHZ): 7.40 (m, 1H), 7.37 (m, 1H), 7.20 (app t, $J = 7.8, 1\text{H}$), 7.15 (m, 1H), 3.55 (t, $J = 7.5, 2\text{H}$), 3.14 (t, $J = 7.5, 2\text{H}$).

Preparation 27

20



Step A:



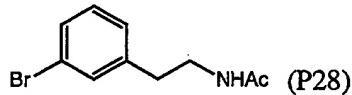
Carbamate P27 was prepared from 3-bromophenylacetonitrile, according to the procedure described for the synthesis of Preparation 19, in a combined yield of 65.7 %.
¹H NMR: 7.39-7.38 (m, 2H), 7.25 (m, 1H), 7.20 (app d, J = 7.6, 1H), 6.87 (br m, 1H), 3.14 (app q, J = 6.3, 2H), 2.69 (t, J = 7.2, 2H), 1.35 (s, 9H). (ESI) m/z (M+Na)⁺ = 5 322.06/324.06.

Step B:

If required, the amine intermediate P27A could be isolated by preparing a silica gel mesh from the crude material obtained from the reduction step of Preparation 19 and 10 submitting it to flash chromatography (EtOAc; 20 % MeOH/CHCl₃). ¹H NMR: 7.42 (m, 1H), 7.39-7.37 (m, 1H), 7.24 (app t, J = 7.7, 1H), 7.22-7.20 (m, 1H), 2.76 (t, J = 7.2, 2H), 2.63 (t, J = 7.2, 2H), 1.75 (br s, 2H). (ESI) m/z (M+H)⁺ = 200.09/202.09.

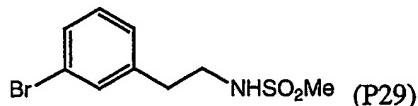
Preparation 28

15



TEA (400 uL, 2.8698 mmol) and acetic anhydride (230 uL, 2.4377 mmol) were added into a THF (5.0 mL) solution of amine P27A (311.6 mg, 1.5574 mmol), and the 20 reaction mixture was stirred at rt for 15.5 h. The volatile component was removed *in vacuo*, and a silica gel mesh of the crude material was prepared and submitted to flash chromatography (50-60 % EtOAc/hexanes) to afford bromide P28 as an off-white solid (285.3 mg, 75.7 %). ¹H NMR: 7.90 (m, 1H), 7.42 (m, 1H), 7.40 (m, 1H), 7.26 (app t, J = 7.8, 1H), 7.21 (m, 1H), 3.25 (m, 2H), 2.70 (t, J = 7.4, 2H), 1.77 (s, 3H). (ESI) m/z (M+H)⁺ = 242.11/244.11.

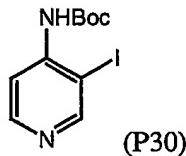
Preparation 29



Methanesulfonyl chloride (140 uL, 1.8088 mmol) was added dropwise over 1 min. to a cooled (0°C) CH₂Cl₂ (5.0 mL) solution of amine P27A (297.7 mg, 1.49 mmol).

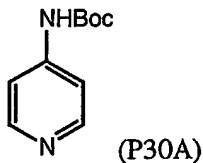
- 5 The reaction mixture was stirred for 15 h while the bath was allowed to thaw. The solvent was removed *in vacuo*, and a silca gel mesh of the residue was prepared and submitted to flash chromatography (30-40 % EtOAc/hexanes) to afford sulfonamide P29 as a colorless viscous oil (317.8 mg, 76.8 %). ¹H NMR: 7.48 (m, 1H), 7.42 (m, 1H), 7.29-7.25 (m, 2H), 7.08 (t, J = 5.8, 1H), 3.18 (m, 2H), 2.84 (s, 3H), 2.76 (t, J = 7.4, 2H). (ESI) 10 m/z (M+H)⁺ = 278.08/280.08.

Preparation 30



15

Step A:



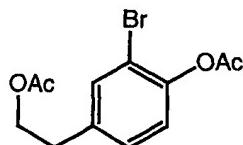
- 20 NaH (1.34 g of 60 %, 33.50 mmol) was added in portions over 10 min. to a THF (60 mL) solution of 4-aminopyridine (3.07g, 32.62 mmol), and the reaction mixture was stirred for 1 hr. Di-*tert*-butyldicarbonate (7.32 g, 33.54 mmol) followed by additional THF (30 mL) were added and the mixture was stirred overnight. It was then diluted with

water and extracted with EtOAc. The organic layer was washed with brine, dried (MgSO_4), filtered, and evaporated *in vacuo*. The resulting solid was recrystallized from EtOAc/hexanes to afford carbamate P30A as a light pink crystalline solid (5.97 g, 94.2 %). ^1H NMR (CDCl_3 , δ = 7.26 ppm; 300 MHZ): 8.43 (d, J = 6.3, 2H), 7.31 (d, J = 6.4, 2H), 6.93 (br s, 1H), 1.52 (s, 9H). (ESI) m/z (M+H) $^+$ = 195.0.

Step B:

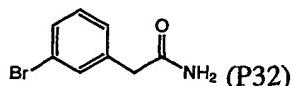
Butyllithium (8.10 mL of 1.6 M/hexanes, 12.96 mmol) was added dropwise to a cooled (-78°C) THF (15.0 mL) solution of carbamate P30A (1.00 g, 5.149 mmol) and TMEDA (1.96 mL, 13.00 mmol). 15 min. later, the -78°C bath was replaced with a -10°C bath, and the reaction was stirred for 2 h. The yellow suspension was cooled back to -78°C and treated dropwise with a THF (13.0 mL) solution of I_2 (3.30 g, 13 mmol). The reaction mixture was stirred at -78°C for 2 h, and the cooling bath was removed and the reaction quenched with a THF/H₂O solution. The mixture was extracted with ether; the organic layer was washed with an aqueous sodium bisulfite solution and brine, dried (MgSO_4), filtered and evaporated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (5 % MeOH/EtOAc) to afford iodide P30 as a yellow oil (1.27 g, 77.1 %). ^1H NMR (CDCl_3 , δ = 7.26 ppm; 300 MHZ): 8.75 (s, 1H), 8.34 (d, J = 5.6, 1H), 8.10 (d, J = 5.6, 1H), 7.04 (br s, 1H), 1.54 (s, 9H). (ESI) m/z (M+H) $^+$ = 320.9.

Preparation 31



Preparation 31 was prepared from 2(3'-bromo-4'-hydroxyphenyl)ethanol by protection of both alcohol groups as described above for Preparation 10.

Preparation 32

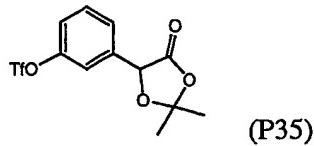


Anhydrous ammonia was bubbled through a MeOH (50.0 mL) solution of Preparation 25 (2.34g, 10.21 mmol) in a Parr-bomb for 10 min. The apparatus was capped and heated at 100 °C for 28 h. After it was allowed to cool to room temperature, the volatile component was removed *in vacuo*, and a silica gel mesh was prepared from the residue and submitted to flash chromatography (EtOAc) to afford amide P32 as an off-white fluffy solid (1.887g, 86.3%). ¹H NMR (500 MHZ): 7.50 (br s, 1 H), 7.47 (s, 1H), 7.42 (m, 1H), 7.28-7.25 (m, 2H), 6.92 (br s, 1H), 3.38 (s, 2H). (ESI) m/z (M+H)⁺ = 213.99/215.99.

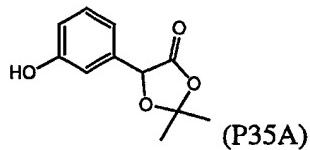
Preparation 33 -34

Ester 33 and amide 34, shown in the table below, were prepared from 3-(3-bromophenyl) propionic acid according to the procedure described for the synthesis of ester 25 and amide 32, respectively.

Pre. #		(M+H) ⁺	Other Data (¹ H NMR)
P33			(CDCl ₃ , 500 MHZ): 7.35-7.33 (m, 2H), 7.17-7.12 (m, 2H), 3.68 (s, 3H), 2.92 (t, J = 7.77, 2H), 2.62 (t, J = 7.77, 2H).
P34		227.94/ 229.94	(500 MHZ): 7.42 (s, 1H), 7.37 (m, 1H), 7.28 (br s, 1H), 7.25-7.21 (m, 2H), 6.77 (br s, 1H), 2.79 (t, J = 7.5, 2H), 2.35 (t, J = 7.5, 2H).

Preparation 35

5 Step A:



Benzene (10 mL) and 2,2-dimethoxypropane (900 uL, 7.319 mmol) were added into a flask containing hydroxy-(3-hydroxy-phenyl)-acetic acid (1.073 g, 6.38 mmol).

10 The flask was equipped with a Dean-Stark apparatus, and the heterogeneous reaction mixture was refluxed for 2.75 h and allowed to cool to room temperature. Silica gel was added and the volatile component was removed *in vacuo* and the resulting silica gel mesh was submitted to flash chromatography (20-30 % EtOAc/hexanes) to afford phenol P35A as a viscous faint yellow oil (1.196 g, 90%). ¹H NMR (CDCl₃, 500 MHZ): 7.29-7.26 (m, 1H), 7.04 (m, 1H), 6.94 (m, 1H), 6.83 (m, 1H), 5.34 (s, 1H), 4.99 (br s, 1H), 1.72 (s, 3H), 1.67 (s, 3H).

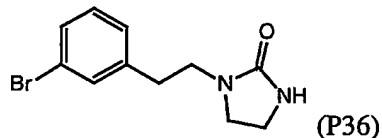
Step B:

20 2-[*N,N*-Bis(trifluoromethylsulfonyl)amino]pyridine (1.3298 g, 3.7120 mmol) was added in one batch to an ice-water cooled CH₂Cl₂ (10.0 mL) solution of Et₃N (700 uL, 5.0222 mmol) and alcohol P35A (693.8 mg, 3.3322 mmol) and stirred for 45 min. The cooling bath was removed and the reaction mixture was stirred for an additional 80 min. Silica gel was added and the volatile component was removed *in vacuo*, and the resultant silica gel mesh was submitted to flash chromatography (15% EtOAc/hexanes) to afford 25 triflate P35 as an oil (1.0407g, 92%). ¹H NMR (CDCl₃, 500 MHZ): 7.57 (d, *J* = 7.2, 1H),

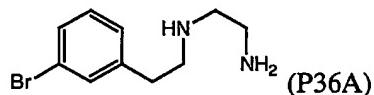
7.51 (app t, $J = 8.0$, 1H), 7.45 (br s, 1H), 7.29 (dd, $J = 2.3$, 1H), 5.43 (s, 1H), 1.72 (s, 3H), 1.70 (s, 3H).

Preparation 36

5



Step A:

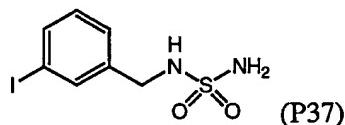


10

Preparation 26 (1.0149 g, 3.845 mmol) was added to ethylenediamine (51.0 mL) and the resulting solution was heated at 70 °C for 4.75 h. All the volatile component was removed *in vacuo*, and the crude oil was triturated with EtOAc, filtered and the filtrate was rotavaped. The crude material was submitted to Prep-HPLC to afford a TFA (2x) salt of dimaine P36A as a yellow oil. The salt was free-based according to the procedure described in Examples 159-173 (297 mg). (ESI) m/z (M+H)⁺ = 243.01/245.01.

Step B:

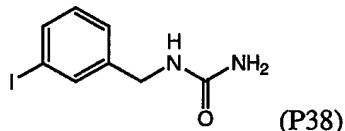
Carbonyl diimidazole (218.4 mg, 1.3469 mmol) was added in one batch to a THF (7.0 mL) solution of the above diamine, and stirred for 23 h. The volatile component was removed *in vacuo* and the residue was loaded onto an SCX column (pre-equilibrated with MeOH) and eluted with MeOH. The solvent was removed *in vacuo* to afford urea P36 along with imidazole impurity in a 6.5 to 1.0 mole ratio (¹H NMR), respectively. The solid weighed 322.7 mg. ¹H NMR: 7.46 (br s, 1H), 7.39 (m, 1H), 7.27-7.24 (m, 2H), 6.26 (s, 1H), 3.31-3.26 (m, 4H), 3.18 (m, 2H), 2.74 (t, $J = 7.3$, 2H). (ESI) m/z (M+H)⁺ = 268.99/270.99.

Preparation 37

5 Sulfamide (2.08 g, 21.65 mmol) was added in one batch to a dioxane (20.0 mL) solution of 3-iodobenzylamine (1.060 g, 4.548 mmol), and the reaction mixture was heated at 90 °C until the benzylamine was totally consumed (> 20 h). The volatile component was removed, and a silica gel mesh was prepared from the residue and submitted to flash chromatography (40-50 % EtOAc/hexanes) to afford sulfamide P37 as
10 a white solid (1.05 g, 74.0%). ^1H NMR: 7.74 (s, 1H), 7.61 (d, J = 8.0, 1H), 7.36 (d, J = 7.5, 1H), 7.15-7.10 (m, 2H), 6.65 (s, 2H), 4.04 (d, J = 6.5, 2H). (ESI) m/z (M+Na) $^+$ = 334.90.

Preparation 38

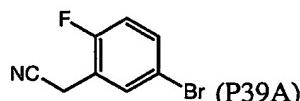
15



Acetic acid (1.30 mL, 22.71 mmol) was added into a mixture of 3-
15 iodobenzylamine (1.00 g, 4.30 mmol) and potassium cyanate (1.707 g, 21.04 mmol), and
20 the reaction mixture was stirred for 75 min. All the volatile component was removed *in vacuo*, and a silica gel mesh was prepared from the residue and submitted to flash chromatography (0-10% MeOH/EtOAc) to afford urea P38 as a white fluffy solid (1.139 g, 96%). ^1H NMR: 7.61 (s, 1H), 7.58 (d, J = 8.0, 1H), 7.26 (d, J = 8.0, 1H), 7.12 (t, J = 7.8, 1H), 6.45 (br t, J = 5.8, 1H), 5.55 (s, 2H), 4.13 (d, J = 6.0, 2H). (ESI) m/z (M+H) $^+$ =
25 276.97.

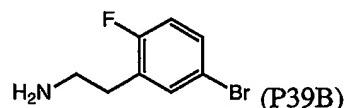
Preparation 39

5 Step A:



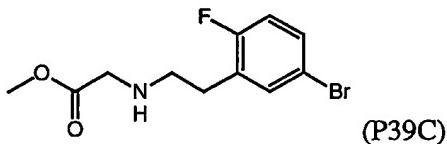
Bromide P39A was prepared from 5-Bromo-2-fluorotoluene according to PCT US 00 11643.

10 Step B:



$\text{BH}_3\cdot\text{SMe}_2$ (8.0 mL, 16.0 mmol) was added to a THF (20.0 mL) solution of bromide P39A (2.26 g, 10.56 mmol). The reaction mixture was refluxed for 10 h, allowed to cool to room temperature, treated with MeOH (15.0 mL) and concentrated HCl (3.0 mL) and stirred overnight. It was heated at 75 °C for 37 min, allowed to cool to room temperature and concentrated *in vacuo*. The residue was diluted with 1N HCl and washed with ether. The aqueous phase was carefully neutralized with solid NaOH, and extracted with CH_2Cl_2 (2x). The combined organic phase was washed with brine, dried (MgSO_4), filtered and evaporated *in vacuo* to afford amine P39B as a colorless oil (1.682g). ^1H NMR: 7.51 (dd, $J = 6.5, 2.5$, 1H), 4.42 (ddd, $J = 8.8, 4.5, 2.8$, 1H), 7.13 (app t, $J = 9.3$, 1H), 2.75 (app t, $J = 7.0$, 2H), 7.3 (app t, $J = 7.3$, 2H), 1.71 (br s, 2H). (ESI) m/z (M+H) $^+$ = 218.11/220.11.

Step C:



5 Methyl bromoacetate (440 uL, 4.648 mmol) was added dropwise over 1 min to a THF (17.0 mL) solution of amine P39B (1.00g, 4.586 mmol) and Et₃N (2.0 mL, 14.349 mmol), and the reaction mixture was stirred for 15.25 h. About 3 ml of MeOH was added and the volatile component was removed *in vacuo*. The residue was partitioned between EtOAc and water, and the aqueous layer was extracted with EtOAc. The combined
10 organic phase was washed with brine, dried (MgSO₄), filtered and evaporated *in vacuo*. A silica gel mesh of the crude material was submitted to flash chromatography (50-80% EtOAc/hexanes) to afford ester P39C as a colorless oil (975 mg, 73%). ¹H NMR: 7.55 (dd, J = 6.7, 2.7, 1H), 7.42 (ddd, J = 8.8, 4.5, 2.7, 1H), 7.13 (app t, J = 9.4, 1H), 3.61 (s, 3H), 3.35 (s, 2H), 2.75-2.70 (m, 4H), 2.20 (br s, 1H). (ESI) m/z (M+H)⁺ = 290.10/292.10.

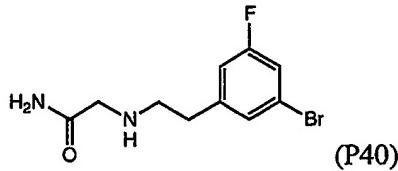
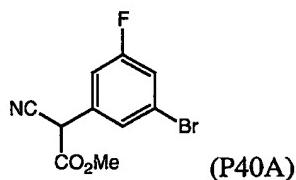
15

Step D

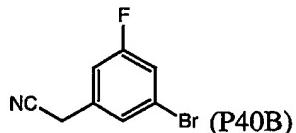
Anhydrous ammonia was bubbled through a MeOH (30 mL) solution of ester P39C, in a Parr-bomb, for 10 min. The apparatus was capped and heated at 61 °C for 20 h. The volatile component was removed *in vacuo*, a silica gel mesh was prepared from
20 the residue and submitted to flash chromatography (5-10% MeOH/EtOAc) to afford amide P39 as an off-white solid (826.8 mg, 89.6%). ¹H NMR: 7.54 (dd, J = 6.7, 2.7, 1H), 7.43 (m, 1H), 7.18 (br s, 1H), 7.14 (app t, J = 9.2, 1H), 7.02 (br s, 1H), 3.05 (s, 2H), 2.74-2.69 (m, 4H). (ESI) m/z (M+H)⁺ = 275.04/277.04.

25

Preparation 40

**Step A:**

Ester P40 was prepared from Bromo-3,5-difluorobenzene according to Synthesis, 1997, p. 1411.

10 Step B:

DMSO (64.0 mL) and water (700 uL) were added into a mixture of NaCl (387.8 mg, 6.4676 mmol) ester P40A (5.45 g, 19.05 mmol), and the reaction mixture was heated 15 at 160 °C for 4 h—a vigorous evolution of gas was observed. After it was allowed to cool to room temperature, it was diluted with water (100 mL) and extracted with ether (100 mL, 3x) with a gentle shaking to prevent emulsification. HCl (1.0 mL of 1N) was added to the aqueous phase and additional ether extraction was conducted (100 mL, 2x). The combined organic phase was washed with brine, dried (MgSO_4), filtered and evaporated 20 *in vacuo*. A silica gel mesh was prepared and submitted to flash chromatography (7.5% EtOAc/hexanes) to afford nitrile P40B as a faint yellow oil (3.69 g, 86.1%). ^1H NMR:

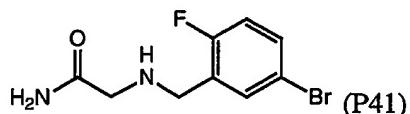
7.56 (dt, $J = 8.5, 2.1$, 1H), 7.46 (br s, 1H), 7.28 (app d, $J = 9.5$, 1H), 4.10 (s, 2H). (ESI) m/z (M-H)⁻ = 211.84/213.84.

Step C:

Nitrile P40B was elaborated to amide P40 through a three step procedure described in the synthesis amide P39. ¹H NMR: 7.35 (dt, $J = 7.4, 2.0$, 1H), 7.31 (app br s, 1H), 7.17 (br s, 1H), 7.14 (m, 1H), 7.01 (br s, 1H). 3.04 (s, 2H), 2.71 (s, 4H), 2.30 (br s, 1H). (ESI) m/z (M+H)⁺ = 275.10/277.10.

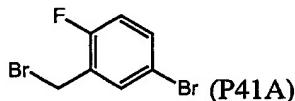
10

Preparation 41



Step A:

15



Dibromide P41A was prepared from 5-Bromo-2-fluorotoluene according to PCT US 00 11643.

20

Step B:

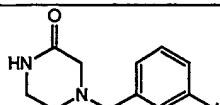
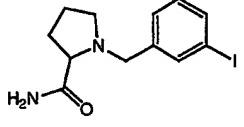
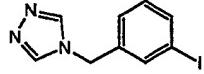
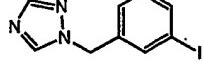
Dibromide P41A (1.048 g, 3.910 mmol), HCl salt of $\text{H}_2\text{NCH}_2\text{CONH}_2$ (1.632 g, 14.76 mmol), K_2CO_3 (2.736 g, 19.80 mmol) and DMF (30 mL) were sequentially added into a flask and the mixture was heated at 60 °C 3.75 h, and allowed to cool to room temperature. All the volatile component was removed *in vacuo*, and the residue was partitioned between 50 % saturated NaCl and EtOAc. The aqueous phase was extracted with EtOAc, and the combined organic phase was washed with brine, dried (MgSO_4),

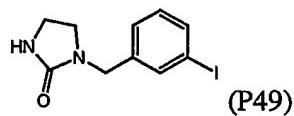
filtered and evaporated *in vacuo*. A silica gel mesh was prepared and submitted to flash chromatography (0-5% MeOH/EtOAc) to afford amide P41 as a white solid (614.4 mg, 60.2%). ¹H NMR: 7.68 (dd, *J* = 6.6, 2.6, 1H), 7.48 (ddd, *J* = 8.7, 4.7, 2.7, 1H), 7.30 (br s, 1H), 7.16 (dd, *J* = 9.8, 8.6, 1H), 7.05 (br s, 1H), 3.7 (s, 2H), 3.05 (s, 2H), 2.79 (br s, 1H).
 5 (ESI) m/z (M+H)⁺ = 261.08/263.08.

Preparation 42-48

Amides 42-48 were prepared from 3-iodobenzyl bromide according to the
 10 procedure described for amide P41. The use of 1,2,4-triazole afforded the regioisomeric iodides 47 and 48.

Pre. #		(M+H) ⁺	Other Data (¹ H NMR)
P42		305.10	7.76 (br s, 1H), 7.62 (d, <i>J</i> = 7.5, 1H), 7.39 (d, <i>J</i> = 7.3, 1H), 7.29 (br s, 1H), 7.13 (app t, <i>J</i> = 7.8, 1H), 7.10 (br s, 1H), 3.51 (s, 2H), 2.89 (s, 2H), 2.15 (s, 3H).
P43		290.96	7.73 (br s, 1H), 7.60 (app d, <i>J</i> = 7.9, 1H), 7.34 (app d, <i>J</i> = 7.6, 1H), 7.29 (br s, 1H), 7.12 (app t, <i>J</i> = 7.6, 1H), 7.04 (s, 1H), 3.64 (s, 2H), 3.01 (s, 2H).
P44		345.00	7.68 (br s, 1H), 7.63 (app d, <i>J</i> = 7.9, 1H), 7.33 (app d, <i>J</i> = 7.9, 1H), 7.14 (app t, <i>J</i> = 7.8, 1H), 3.45 (s, 2H), 3.44-3.40 (m, 4H), 2.34 (app t, <i>J</i> = 5.0, 2H), 2.28 (app t, <i>J</i> = 5.0, 2H), 1.97 (s, 3H).

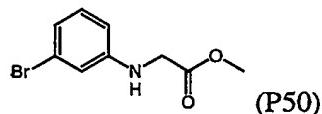
Pre. #		(M+H) ⁺	Other Data (¹ H NMR)
P45		317.01	7.75 (br s, 1H), 7.69 (br s, 1H), 7.64 (app d, <i>J</i> = 7.9, 1H), 7.34 (7.6, 1H), 7.15 (app t, <i>J</i> = 7.8, 1H), 3.50 (s, 2H), 3.16-3.13 (m, 2H), 2.89 (s, 2H), 2.54-2.52 (m, 2H).
P46			7.74 (br s, 1H), 7.61 (app d, <i>J</i> = 7.9, 1H), 7.39 (app d, <i>J</i> = 7.6, 1H), 7.25 (br s, 1H), 7.12 (app t, <i>J</i> = 7.8, 1H), 7.04 (br s, 1H), 3.80 (d, <i>J</i> = 13.4, 1H), 3.32 (signal overlapped with that of water, 1H), 2.94-2.91 (m, 1H), 2.86-2.82 (m, 1H), 2.22-2.17 (m, 1H), 2.08-2.00 (m, 1H), 1.74-1.69 (m, 3H).
P47		285.93	8.62 (s, 2H), 7.71-7.69 (m, 2H), 7.32 (app d, <i>J</i> = 7.9, 1H), 7.18 (app t, <i>J</i> = 7.8, 1H), 5.25 (s, 2H).
P48		285.99	8.67 (s, 1H), 8.00 (s, 1H), 7.69-7.67 (m, 2H), 7.29 (app d, <i>J</i> = 7.6, 1H), 7.17 (app t, <i>J</i> = 7.8, 1H), 5.39 (s, 2H).

Preparation 49

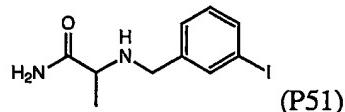
Sodium hydride (60%, 2.74 g, 68.5 mmol) was added to a DMF (100 mL) solution of 2-imidazolidone (5.82 g, 19.6 mmol), and stirred at ambient temperature for 1.5 h. 3-Iodobenzyl bromide (2.01 g, 6.77 mmol) was added and stirring continued for 4 h. It was quenched with methanol and the volatile component was removed *in vacuo*, the residue was partitioned between water and ethyl acetate. Two additional EtOAc extraction of the aqueous layer was conducted. The combined organic phase was dried (MgSO_4), filtered and evaporated *in vacuo*. A silica gel mesh of the residue was submitted to flash chromatography (EtOAc) to afford urea P49 as a white solid (793.7 mg, 38.7 % yield). ^1H NMR: 7.63 (app d, $J = 7.6$, 1H), 7.61 (br s, 1H), 7.26 (app d, $J = 7.9$, 1H), 7.16 (app t, $J = 7.6$, 1H), 6.46 (br s, 1H), 4.19 (s, 2H), 3.25-3.18 (m, 4H). (ESI) m/z (M+H) $^+$ = 302.93.

Preparation 50

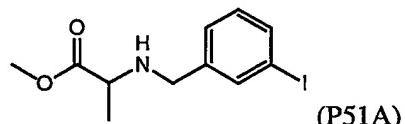
15



Potassium carbonate (1.93 g, 13.9 mmol) was added to a DMF (50 mL) solution of 3-bromoaniline (2.00 g, 11.6 mmol) and methyl bromoacetate (2.15 g, 14.1 mmol), and the reaction mixture was heated at 60 °C for 23h. It was cooled to room temperature and the volatile component was removed *in vacuo*. Water was added to the residue and the product extracted with ethyl acetate. The organic layer was washed with brine, dried (MgSO_4), filtered and evaporated *in vacuo* to afford ester P50 as a white solid (2.8 g; > 95 % yield). The crude was used without further purification. ^1H NMR: 7.01 (app t, $J = 8.1$, 1H), 6.73 (t, $J = 2.0$, 1 H), 6.71-6.70 (m, 1H), 6.54 (dd, $J = 8.4$, 1.7, 1H), 6.31 (t, $J = 6.3$, 1H), 3.93 (d, $J = 6.4$, 2H), 3.65 (s, 3H). (ESI) m/z (M+H) $^+$ = 245.97/243.97.

Preparation 51

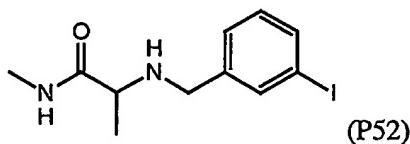
5 Step A:



Ester P51A was prepared from 3-iodobenzyl bromide according to the procedure described for amide P41. ¹H NMR: 7.69 (s, 1H), 7.58 (app d, J = 7.6, 1H), 7.31 (app d, J = 7.3, 1H), 7.11 (app t, J = 7.6, 1H), 3.69 (d, J = 13.7, 1H), 3.62 (s, 3H), 3.55 (d, J = 14.1, 1H), 3.26 (m, 1H), 2.58 (br s, 1H), 1.20 (d, J = 7.0, 3H). (ESI) m/z (M+H)⁺ = 320.08.

Step B:

Aminolysis of ester P51A was conducted according to the procedure described for the synthesis of amide P39. ¹H NMR (400 MHZ): 7.72 (s, 1H), 7.59 (app d, J = 7.6, 1H), 7.35-7.33 (m, 2H), 7.12 (app t, J = 7.8, 1H), 6.98 (br s, 1H), 3.65 (d, J = 14.0, 1H), 3.50 (d, J = 14.0, 1H), 2.99 (q, J = 6.8, 1H), 1.13 (d, J = 7.2, 3H). (ESI) m/z (M+H)⁺ = 305.06.

Preparation 52

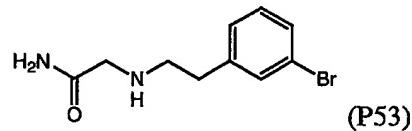
20

MeNH₂ (20 mL of 40% wt/H₂O) was added into a MeOH (10 mL) solution of ester P51A (1.0091 g, 3.162 mmol) in a Parr-bomb, and the reaction mixture was heated at 60 °C for 22.25 h. After it was allowed to cool to room temperature, all the volatile

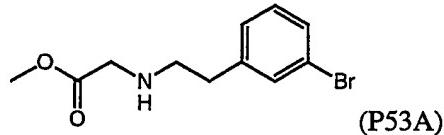
component was removed *in vacuo*. A silica gel mesh was prepared from the residue and submitted to flash chromatography (0-2% MeOH/EtOAc) to afford amide P52 as a viscous oil (728 mg, 72.4%). ¹H NMR: (400 MHZ): 7.78 (m, 1H), 7.73 (s, 1H), 7.59 (d, J = 8.0, 1H), 7.34 (d, J = 7.6, 1H), 7.11 (app t, J = 7.6, 1H), 3.62 (d, J = 14.0, 1H), 3.49 (d, J = 14.0, 1H), 3.00 (q, J = 6.8, 1H), 2.60 (d, J = 4.8, 3H), 1.12 (d, J = 6.8, 3H). (ESI) m/z (M+H)⁺ = 319.04.

Preparation 53

10



Step A:



15

Ester P53A was prepared from amine P27A according to the procedure described for the synthesis of ester P39C. ¹H NMR: 7.44 (s, 1H), 7.38-7.36 (m, 1H), 7.25-7.21 (m, 2H), 3.61 (s, 3H), 3.34 (s, 2H), 2.76-2.67 (m, 4H), 1.98 (br s, 1H). (ESI) m/z (M+H)⁺ = 272.03/274.03.

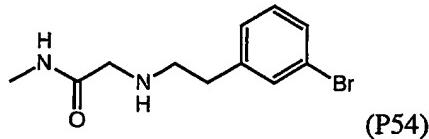
20

Step B:

Conversion of ester P53A to amide P53 was conducted according to the procedure described for the synthesis of ester P39C. ¹H NMR: 7.43 (s, 1H), 7.38 (app td, J = 6.5, 2.3, 1H), 7.26-7.23 (m, 2H), 7.17 (br s, 1H), 7.00 (br s, 1H), 3.04 (s, 2H), 2.69 (s, 4H), 2.07 (br s, 1H). (ESI) m/z (M+H)⁺ = 257.15/259.15.

25

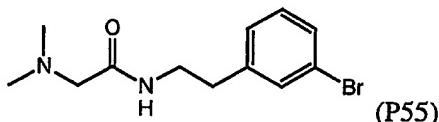
Preparation 54



Ester P53A was converted to amide P54 according to the procedure described for
 5 the synthesis of amide P52. ^1H NMR: 7.61 (br s, 1H), 7.43 (br s, 1H), 7.39 (app dt, $J = 7.3, 1.8, 1\text{H}$), 7.26-7.22 (m, 2H), 3.07 (s, 2H), 2.69 (s, 4H), 2.57 (d, $J = 4.5, 3\text{H}$). (ESI)
 m/z $(\text{M}+\text{H})^+ = 271.09/273.09$.

Preparation 55

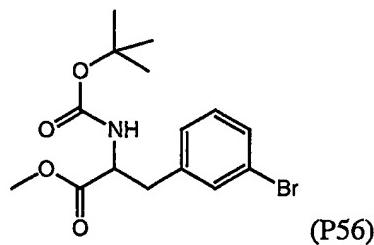
10



The HCl salt of $\text{Me}_2\text{NCH}_2\text{COCl}$ (1.02 g, 6.454 mmol) was added into a DMF
 (20.0 mL) solution of amine P27A (602 mg, 3.009 mmol) and Et_3N (3.0 mL, 21.52
 15 mmol) and the heterogeneous mixture was sonicated for 1 min and vigorously stirred
 until the starting material is completely consumed. The volatile component was removed
in vacuo and residue was partitioned between EtOAc and dilute NaHCO_3 solution. The
 aqueous layer was extracted with EtOAc, and the combined organic phase was washed
 with brine, dried (MgSO_4), filtered and evaporated *in vacuo*. The resulting viscous oil
 20 was directly submitted to flash chromatography (0-2% MeOH/EtOAc) to afford bromide
 P55 as light red oil (451.5 mg, 52.6%). ^1H NMR: 7.76 (br m, 1H), 7.41-7.38 (m, 2H),
 7.26-7.22 (m, 2H), 3.35-3.29 (m, 2H), 2.80 (s, 2H), 2.75 (app t, $J = 7, 2\text{H}$), 2.14 (s, 6H).
 (ESI) m/z $(\text{M}+\text{H})^+ = 285.12 / 287.12$.

25

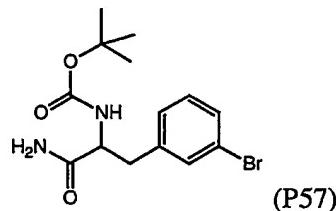
Preparation 56



N-Boc-3-bromophenylalanine was converted to ester P56 according to the procedure described for the synthesis of ester P25. ¹H NMR: 7.45 (br s, 1H), 7.42-7.40 (m,1H), 7.32 (d, J = 8.3, 1H), 7.25 (m, 2H), 4.21-4.18 (m, 1H), 3.62 (s, 3H), 3.02 (dd, J = 13.8, 4.6, 1H), 2.84 (dd, J = 13.7, 10.4, 1H), 1.32 (s, 9H). (ESI) m/z (M+Na)⁺ = 379.97/381.97.

Preparation 57

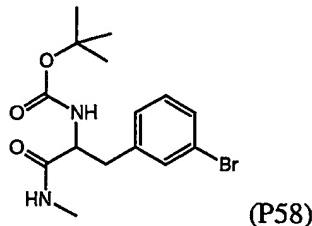
10



Anhydrous ammonia was bubbled through a MeOH (10.0 mL) solution of ester P56 (305.2 mg, 0.852 mmol) for 30 min, and the reaction mixture was stirred at ambient temperature for 63 h. Removal of the volatile component *in vacuo* afforded amide P57 as an off-white solid (290 mg, >95%). The product was used without further purification. ¹H NMR: 7.48 (br s, 1H), 7.39-7.38 (m, 2H), 7.28-7.22 (m, 2H), 7.03 (br s, 1H), 6.85 (d, J = 8.9, 1H), 4.10-4.06 (m, 1H), 2.96 (dd, J = 13.7, 4.0, 1H), 2.71 (dd, J = 13.7, 10.7, 1H), 1.30 (s, 9H). (ESI) m/z (M+Na)⁺ = 364.98/366.98

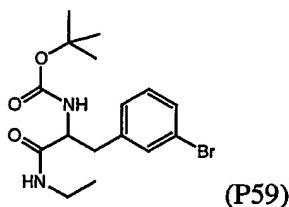
20

Preparation 58



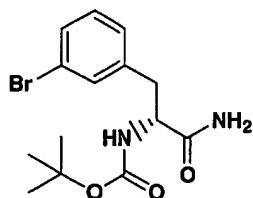
Methylamine (15 mL of 40 wt % in water) was added to a MeOH (5.0 mL) solution of ester P58 (248.7 mg, 0.7225 mmol), and the reaction mixture was stirred at ambient temperature for 6 days. Removal of the volatile component *in vacuo* afforded amide P58 as an off-white solid (185 mg; it is not apparent why the yield is not quantitative). The product was used without further purification. ^1H NMR: 7.86 (br m, 1H), 7.46 (app s, 1H), 7.38 (app d, J = 6.4, 1H), 7.24-7.21 (m, 2H), 6.95 (d, J = 8.5, 1H), 4.2 (m, 1H), 2.93 (dd, J = 13.6, 4.2, 1H), 2.70 (m, 1H), 2.59 (d, J = 4.2, 3 H), 1.29 (s, 9H). (ESI) m/z (M+Na) $^+$ = 381.04/379.04

Preparation 59



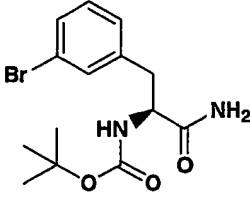
15

Ethylamine (15.0 mL of 70 wt. % in water) was added to a methanol (5.0 mL) solution of ester P56 (252.1 mg, 0.7324 mmol), and the reaction mixture was stirred at 25 °C for 68 h. Removal of the volatile component *in vacuo* afforded amide P59 as an off-white solid (270 mg; this is 8.6 mg above the theoretical yield). The product was used without further purification. ^1H NMR: 7.89 (app br t, J = 5.2, 1H), 7.46 (br s, 1H), 7.38 (m, 1H), 7.26-7.21 (m, 2H), 6.90 (app d, J = 8.8, 1H), 4.09-4.05 (m, 1H), 3.11-3.02 (m, 2H), 2.91 (dd, J = 13.6, 4.5, 1H), 2.71 (dd, J = 13.5, 10.4, 1H), 1.30 (s, 9H), 0.98 (t, J = 7.2, 3H). (ESI) m/z (M-Boc+H) $^+$ = 273.09/271.09

Preparation 60 and 61

5

(P60)

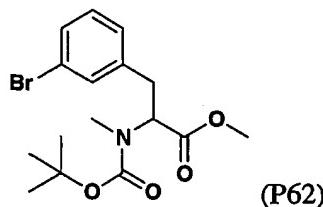


(P61)

Isobutyl chloroformate (87.4 mg, 0.640 mmol) was added to a cooled (-30 °C) CH₂Cl₂ (3.0 mL) solution of (R)-N-Boc-3-bromophenylalanine (202.0 mg, 0.5869 mmol) and N-methylmorpholine (64.8 mg, 0.641 mmol). After the reaction mixture was allowed 10 to warm up to -20 °C over 30 min, ammonia was bubbled through it for 15 min. The cold bath was removed and the reaction mixture was stirred for an additional 1 hr. It was then partitioned between water and CH₂Cl₂, and the aqueous phase was extracted with CH₂Cl₂. The combined organic phase was dried (Na₂SO₄), filtered, and concentrated *in vacuo* to afford amide P60 as an off-white solid (200 mg, >95% yield). The product was 15 used without further purification. . ¹H NMR: (see the data for P57). (ESI) m/z (M+Na)⁺ = 365.16/367.16.

The (S) enantiomer (P61) was synthesized by employing the same procedure. . ¹H NMR: (see the data for P57). (ESI) m/z (M+Na)⁺ = 365.14/367.16

20

Preparation 62

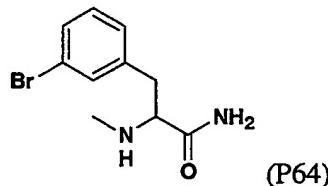
Sodium hydride (400 mg of 60%, 10 mmol) was added to a cooled, -10 °C, DMF (25 mL) solution of *N*-BOC-(3-bromophenyl)alanine (1.49 g, 4.32 mmol). After the mixture was stirred at -10 °C for 0.5h, methyl iodide (1.6 g, 67 mmol) was added; the bath 5 temperature was allowed to reach 0 °C and the reaction mixture was stored in a refrigerator (~6 °C) for 29 h. It was quenched with water (50 mL) at 0 °C, and the product was extracted with ethyl acetate (100 mL, 3x). The combined organic phase was washed with water (50 mL, 3x), saturated aqueous sodium bicarbonate, brine (50 mL), and dried (MgSO_4), filtered and evaporated *in vacuo*. The resultant crude material was 10 submitted to flash chromatography (0-25 % EtOAc/hexanes) to afford ester P62 as an oil (1.5 g, 93% yield). ^1H NMR: 7.47-7.39 (m, 2H), 7.27-7.21 (m, 2H), 4.85-4.71 (m, 1H), 3.69 and 3.67 (s, 3H), 3.18 (dd, $J = 14, 4.6$, 1H), 3.07-2.97 (m, 1H), 2.60 and 2.57 (s, 3H), 1.32 and 1.25 (s, 9H). (ESI) m/z (M+Na) $^+$ = 394.05/396.05

15

Preparation 63

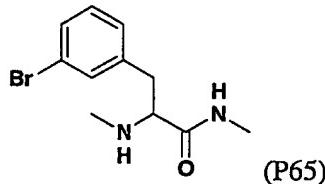
A TFA/CH₂Cl₂ (20%; 25 mL) solution of carbamate P62 (1.50 g, 4.0 mmol) was stirred 20 at ambient temperature for 1 h. The volatile component was removed *in vacuo* and the residue was dissolved in MeOH and loaded onto an SCX column (preconditioned with MeOH). The column was first washed with MeOH and then with 2N NH₃/methanol to afford amine P63 as a viscous oil (1.10; >95 %). ^1H NMR (400): 7.40-7.38 (m, 2H), 7.25-7.18 (m, 2H), 3.58 (s, 3H), 3.35 (app t, $J = 7.1$, 1H), 2.28 (app d, $J = 7.1$, 2H), 2.20 25 (s, 3H), 2.09 (br s, 1H). (ESI) m/z (M+H) $^+$ = 272.06/274.06.

Preparation 64



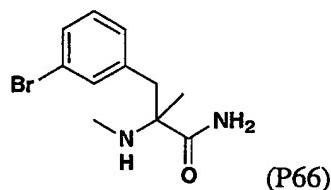
Anhydrous ammonia was bubbled through a MeOH (30 mL) solution of ester P63
 5 (287.9 mg, 1.058 mmol) in a Parr-bomb for 10 min. The apparatus was capped and heated
 at 60 °C until the starting material was totally consumed (>2 days). The volatile
 component was removed *in vacuo*, and a silica gel mesh was prepared from the residue
 and submitted to flash chromatography (5 % MeOH/CHCl₃) to afford amide P64 as a
 white solid (180 mg, 66.2 %). ¹H NMR: 7.42 (br s, 1H), 7.39-7.37 (m, 1H), 7.35 (br s,
 10 1H), 7.24-7.21 (m, 2H), 7.03 (br s, 1H), 3.09 (m, 1H), 2.79 (dd, J = 13.6, 6.0, 1H), 2.67
 (dd, J = 13.6, 8.4, 1H), 2.17 (s, 3H). (ESI) m/z (M+H)⁺ = 257.10/259.10.

Preparation 65

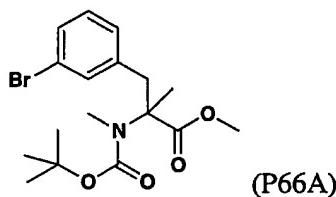


15

Methylamine (20 mL of 40 wt.% in water) was added into a MeOH (10.0 mL)
 solution of ester P63 (294.6 mg, 1.083 mmol) in a Parr-bomb, the apparatus was capped
 and heated at 60 °C for 8.5 h. After it was cooled to room temperature, the volatile
 20 component was removed *in vacuo*. The residue was loaded onto an SAX column
 (preconditioned with MeOH) and eluted with 2.0 M NH₃/MeOH. A silica gel mesh of the
 resultant product was submitted to a flash chromatography (EtOAc) to afford amide P65
 as colorless oil. (ESI) m/z (M+H)⁺ = 271.16/273.16.

Preparation 66

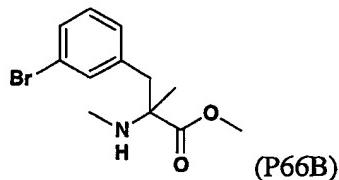
5 Step A:



Sodium hydride (2.7 g of 60%, 67.5 mmol) was added in batches to a cooled, 0
 10 °C, DMF (75 mL) solution of *N*-BOC-(3-bromophenyl)alanine (2.5 g, 7.26 mmol) and
 methyl iodide (14.36 g, 36.47 mmol). The cooling bath was removed and the reaction
 mixture was stirred at ambient temperature for 61 h. It was then poured into water and the
 product was extracted with ethyl acetate (150 mL, 3x). The combined organic layer was
 washed with water (3 x 50 mL) and brine, dried (MgSO_4), filtered and evaporated *in*
 15 *vacuo*. A silica gel mesh of the crude material was submitted to flash chromatography
 (75% hexanes/ethyl acetate) to afford ester P66A as a colorless oil (1.9 g, 68%). ^1H
 NMR: 7.47-7.45 (m, 1H), 7.30-7.26 (app t, $J = 7.8$, 2H), 7.12 (app d, $J = 7.3$, 1H), 3.36
 (br s, 3H), 3.43 (br s, 1H), 2.89 (br s, 1H), 2.39 (br s, 3H), 1.40 (br s, 9H), 1.31 (br s, 3H).
 (ESI) m/z ($\text{M-Boc}+\text{H}$)⁺ = 286.09/288.09.

20

Step B:

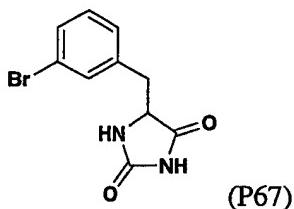


Carbamate P66A was deprotected and free-based according to the procedure described in the synthesis of ester P63. ¹H NMR: 7.42-7.40 (m, 1H), 7.34 (m, 1H), 7.23 (app t, J = 7.8, 1H), 7.14 (app d, J = 7.6, 1H), 3.62 (s, 3H), 2.83 (s, 2H), 2.16 (s, 3H), 1.06 (s, 3H). (ESI) m/z (M+H)⁺ = 286.09/288.09.

Step C

Anhydrous ammonia was bubbled through a MeOH (30 mL) solution of ester P66B (287.9 mg, 1.06 mmol) in a Parr-bomb, and the apparatus was capped and heated at 100 °C for 6 days. The volatile component was removed *in vacuo*, and the residue was taken up in CHCl₃ and submitted to flash chromatography (100% CHCl₃ → 5% MeOH/CHCl₃) to afford amide P66 as a white solid (180 mg). ¹H NMR: 7.39-7.36 (m, 2H), 7.23-7.16 (m, 3H), 7.02 (br s, 1H), 2.79 (s, 2H), 2.18 (s, 3H), 1.04 (s, 3H). (ESI) m/z (M+H)⁺ = 271.16/273.16.

Preparation 67



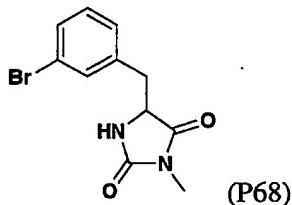
20

Water (5 mL) was added to a mixture of (3-bromophenyl)alanine hydrochloride (1.02 g, 3.64 mmol) and potassium cyanate (325.3 mg, 4.01 mmol), and the mixture was heated at 90 °C for 3.5h. Additional potassium cyanate (650 mg, 8.0 mmol) was added

and stirring continued at 90 °C for 0.5h. The mixture was allowed to cool to room temperature, concentrated HCl (3 mL) was added and then it was heated at 90 °C for 0.5h. After it cooled to room temperature, it was diluted with water and the suspension was filtered and washed with water, and allowed to air dry. Hydantoin P67 was obtained 5 as a tan solid (800 mg, 82% yield). ^1H NMR (400 MHZ): 10.49 (s, 1H), 7.93 (s, 1H), 7.44-7.40 (m, 2H), 7.26 (app t, J = 7.7, 1H), 7.19 (m, 1H), 4.37-4.34 (m, 1H), 2.96 (dd, J = 13.9, 4.9, 1H), 2.90 (dd, J = 14.0, 5.4, 1H). (ESI) m/z ($\text{M}+\text{H}$)⁺ = 269.08/271.08.

Preparation 68

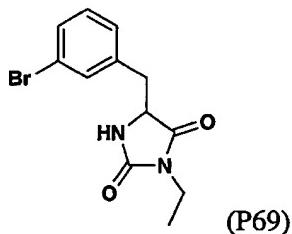
10



Hydantoin P67 was methylated according to the procedure described for the synthesis of ester P25. It was obtained as an off-white solid. ^1H NMR: 8.23 (br s, 1H), 15 7.43 (app d, J = 7.9, 1H), 7.39 (m, 1H), 7.25 (app t, J = 7.8, 1H), 7.18 (app d, J = 7.6, 1H), 4.38 (m, 1H), 2.99 (dd, J = 14, 4.9, 1H), 2.90 (dd, J = 14, 6.1, 1H), 2.69 (s 3H). (ESI) m/z ($\text{M}+\text{H}$)⁺ = 283.08/285.08.

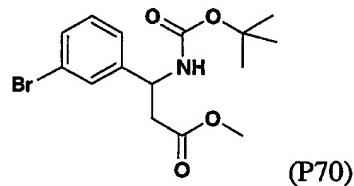
Preparation 69

20



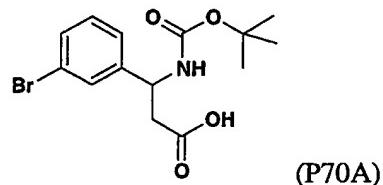
DMF (3.0 mL) followed by ethyl iodide (104.4 mg, 0.6694 mmol) were added to a mixture of hydantoin P67 (149.4 mg, 0.5552 mmol) and potassium carbonate (92.8 mg, 0.671 mmol). The reaction mixture was heated at 90 °C for 20h, cooled to room temperature, and all the volatile component was removed *in vacuo*. The residue was 5 diluted with water and extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with water and brine, dried (MgSO_4), filtered and evaporated *in vacuo* to afford hydantoin P69 as an off-white solid (150 mg, 91% yield). The product was used without further purification. ^1H NMR: 8.22 (br s, 1H), 7.42 (app d, $J = 8.3$, 1H), 7.35 (m, 1H), 7.24 (app t, $J = 7.8$, 1H), 7.17 (app d, $J = 7.7$, 1H), 4.37 (t, $J = 4.6$, 1H), 3.27-3.13 10 (m, 2H), 2.96 (d, $J = 4.9$, 2H), 0.77 (t, $J = 6.9$, 3H). (ESI) m/z ($\text{M}+\text{H}$)⁺ = 297.06/299.06.

Preparation 70



15

Step A:



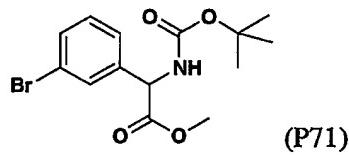
20 A THF (5.0 mL) solution of Boc-anhydride (449.5 mg, 2.060 mmol) was added to a mixture of 3-amino-3-(3-bromophenyl)propanoic acid (503.4 mg, 2.062 mmol) and potassium carbonate (212.4 mg, 2.121 mmol) in water (5 mL). The reaction mixture was stirred at 25 °C for 24h. Additional Boc-anhydride (500 mg, 2.291 mmol) was added and the reaction was stirred at 25 °C for another 18h. Most of the THF was removed *in vacuo*.

and the residue was partitioned between ethyl acetate and water. The aqueous layer was neutralized with 1N HCl, and extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with water (1 x 50 mL) and brine, dried (MgSO_4), filtered and evaporated *in vacuo* to afford carbamate P70A as an oil that solidified upon standing (618mg, 87.1% yield). The product was used without further purification. ^1H NMR: 12.26 (s, 1H), 7.49 (br m, 2H), 7.44-7.42 (m, 1H), 7.31-7.26 (m, 1H), 4.85 (m, 1H), 2.66 (dd, J = 15.7, 8.4, 1H), 2.59 (dd, J = 15.6, 6.7, 1H), 1.35 (s, 9H). (ESI) m/z (M+Na) $^+$ = 366.02/368.02.

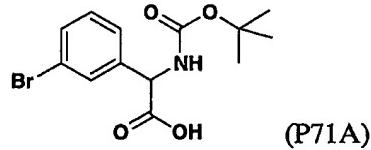
10 Step B:

Ester P70 was prepared from acid P70A according to the procedure described for the synthesis of ester P25. The product was obtained as a colorless oil. ^1H NMR: 7.53-7.51 (m, 2H), 7.44-7.43 (m, 1H), 7.32-7.27 (m, 2H), 4.89 (m, 1H), 3.56 (s, 3H), 2.75 (dd, J = 15.7, 8.7, 1H), 2.69 (dd, J = 15.9, 6.4, 1H), 1.35 (s, 9H). ^1H NMR: (ESI) m/z (M+Na) $^+$ = 379.99/381.99.

Preparation 71



20 Step A:



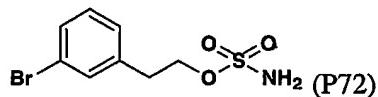
Acid P71A was prepared from 2-amino-2-(3-bromophenyl)acetic acid according to the procedure described for the synthesis of ester P70A. ^1H NMR: 12.93 (br s, 1H), 7.70 (d, J = 8.2, 1H), 7.62 (br s, 1H), 7.51 (d, J = 7.9, 1H), 7.41 (d, J = 7.6, 1H), 7.31 (app t, J = 8, 1H), 5.15 (d, J = 8.5, 1H), 1.39 (s, 9H). (ESI) m/z (M+Na) $^+$ = 353.98 / 351.98.

Step B:

Acid P71A was elaborated to ester P71 according to the procedure described for the synthesis of ester P70. ¹H NMR: 7.89 (d, J = 8.2, 1H), 7.62 (br s, 1H), 7.52 (d, J = 8.0, 1H), 7.40 (d, J = 7.7, 1H), 7.32 (app t, J = 7.9, 1H), 5.27 (d, J = 8.2, 1H), 3.62 (s, 3H), 1.39 (s, 9H). (ESI) m/z (M+Na)⁺ = 365.95/367.95.

Preparation 72

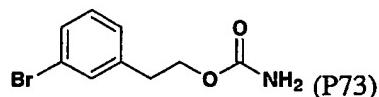
10



Sodium hydride (119.8 mg of 60%, 2.995 mmol) was added to a cooled, 0 °C, DMF (12 mL) solution of 3-bromophenethyl alcohol (0.50 g, 2.5 mmol), and stirred for 45 min. Sulfamoyl chloride (431.5 mg, 3.735 mmol), was added and the mixture was allowed to warm up to room temperature over 15.25 h. The reaction was quenched with methanol, diluted with ethyl acetate (100 mL) and washed with water (3 x 25 mL), and brine. The organic layer was dried (MgSO_4), filtered and evaporated *in vacuo* to afford sulfamate P72 as a white solid (682 mg, >95 %). The product was used without further purification. ¹H NMR: 7.52 (br s, 1H), 7.48 (br s, 2H), 7.45-7.43 (m, 1H), 7.30-7.28 (m, 2H), 4.24 (t, J = 6.7, 2H), 2.98 (t, J = 6.8, 2H). (ESI) m/z (M+Na)⁺ = 301.91/303.91

Preparation 73

25

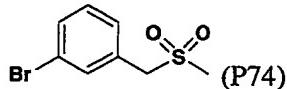


Potassium cyanate (1.68 g, 20.7 mmol) followed by TFA (2.28 g, 20.0 mmol) were added into a CH_2Cl_2 (25.0 mL) a solution of 3-bromophenethyl alcohol (1.01 g, 5.02 mmol),

and the mixture was stirred at 25 °C for 31 h. Water (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (100 mL, 3x). The combined organic phase was washed with brine, dried (MgSO_4) and filtered and evaporated *in vacuo*. The residue was recrystallized (hexanes/ethyl acetate) to afford 5 carbamate P73 as an off-white solid (720 mg, 58.7% yield). $^1\text{H NMR}$: δ 7.47 (br s, 1H), 7.43-7.40 (m, 1H), 7.28-7.24 (m, 2H), 6.51 (br m, 2H), 4.11 (t, J = 6.8, 2H), 2.85 (t, J = 6.8, 2H).

Preparation 74

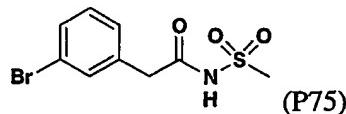
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A mixture of 3-bromobenzyl bromide (3.01 g, 12.0 mmol) and methanesulphinic acid sodium salt (3.12 g, 30.6 mmol) in DMF/water (1:9 v/v, 180 mL) was heated at 45 °C for 15 19.75 h. It was cooled to room temperature and extracted with ethyl acetate (150 mL, 3x). The combined organic phase was washed with water (3 x 50 mL) and brine (100 mL), dried (MgSO_4), filtered and evaporated *in vacuo* to afford sulphone P74 as a white solid (3.00g, >95 %). The product was used without further purification. $^1\text{H NMR}$: 7.62-7.59 (m, 2H), 7.43-7.42 (m, 1H), 7.38 (app t, J = 7.8, 1H), 4.52 (s, 2H), 2.92 (s, 3H).

20

Preparation 75



25 A CH_2Cl_2 (4.0 mL) solution of 1,3-dicyclohexylcarbodiimide (1.25 g, 6.06 mmol) was added over 1 min. to a cooled, 0 °C, mixture of (3-bromophenyl)acetic acid (1.00 g, 4.66 mmol), 4-dimethylaminopyridine (740.0 mg, 6.057 mmol), and methansulfonamide

(575.9 mg, 6.054 mmol) in dichloromethane (17 mL). The mixture was stirred for 20.5h at ambient temperature and filtered, and the filtrate was rotovaped. The residue was submitted to flash chromatography (ethyl acetate; 5% MeOH/CH₂Cl₂) to afford a mixture of sulphonamide P75 and DMAP as a colorless gum (1.8 g; 1:1 mole ratio according to 5 ¹H NMR). The mixture was used for the coupling step with out further purification. ¹H NMR: 7.45 (s, 1H), 7.41-7.39 (m, 1H), 7.26-7.23 (m, 2H), 3.42 (s, 2H), 2.92 (s, 3H). (ESI) m/z (M+H)⁺ = 292.03/294.03.

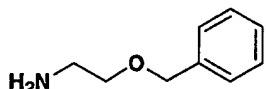
Preparations 76 -78

10

The following compounds were prepared according to the indicated literature procedures:

- 76) 4-Iodo-3-*o*-pyridyl *N,N*-diethylcarbamate: Organic Letters, Vo. 21 (2000) at p. 2291.
- 77) 2-Amino-3-iodopyridine: J. Org. Chem., Vol. 53 (1988) at p. 2740; and
- 15 78) 2-Bromo-1-methyl-1*H*-imidazole: Aust. J. Chem., Vol. 52 (1999) at p. 159.

Preparation 79



20

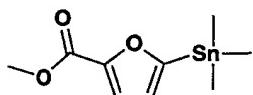
At room temperature, sodium hydride (3.33g, 83.5mmol) was added in small portion to THF (90ml) solution of the ethanolamine (5.04ml, 83.5mmol), and the mixture was stirred under reflux for 30 mins. The reaction mixture was cooled to rt and benzyl chloride (7.7ml, 67.1mmol) was added. The mixture was stirred again under reflux for 15 h. Water (6ml) was added to quench the reaction. The reaction mixture was cooled to rt and solvent was removed *in vacuo*. The residue was dissolved in dichloromethane and washed with water. The organic layer was washed with brine, dried (MgSO₄), filtered and evaporated *in vacuo*. The crude material was submitted to flash chromatography (ethyl acetate, methanol) to afford clear oil (7.57g, 60%). ¹H NMR (DMSO, 400MHZ): 7.32

(m, 5H), 4.47 (s, 2H), 3.39 (t, J=5.8, 2H), 2.69 (t, J=5.8, 2H), 1.51 (br, 2H). (ESI) m/z (M+H)⁺ = 152.21.

Step A:

5

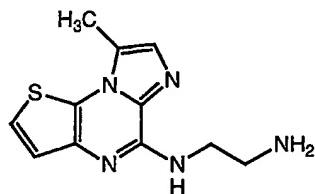
Preparation 80



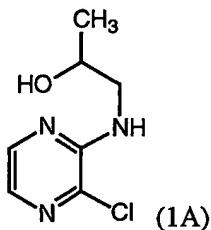
A toluene (10 ml) solution of hexamethylditin (2.924g, 8.93 mmol) was treated
10 with methyl 5-bromo-2-furoate (500mg, 2.44mmol) and triethylamine (0.68mL, 4.88 mmol). After nitrogen was bubbled through the mixture for 5 min, Pd(Ph₃P)₄ (96.0mg, 0.083mmol) was added. The reaction mixture was heated with a 100 °C oil bath for 35 min. The dark reaction mixture was cooled to room temperature, filtered through a pad of Celite, washed with EtOAc, and the filtrate was evaporated in vacuo. The residue was
15 triturated with ether, and the light brown solid was filtered and washed with copious ether and dried in vacuo (490mg of the title compound was retrieved). m/z (M+H)⁺ = 289.

20

Example 1



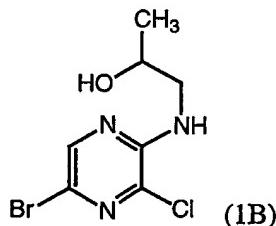
Step A:



1-Amino-2-propanol (25.0 ml, 0.3239 mol) was added to a 1,4-dioxane (81.0 mL) solution of 2,3-dichloropyrazine (19.7 g with 95 % purity, 0.1256 mol). The reaction mixture was heated with an oil bath (pre-equilibrated at 110°C) for 6.75 h. It was then removed from the oil bath and allowed to cool to rt. The two phases were separated, and the upper layer was exposed to vacuum to remove volatile components. The viscous residue was diluted with CH₂Cl₂ and rotovaped a few times to remove residual dioxane and provide the crude compound 1A.

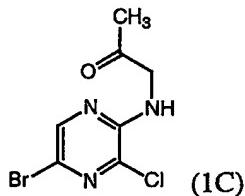
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Step B:



N-Bromosuccinimide (26.09 g, 0.1466 mol) was slowly added to a CHCl₃ (170 mL) solution of crude 1A and the resulting reaction mixture was refluxed for 3.15 h, cooled to rt, washed with water (100 mL, 2x) and brine, and dried over MgSO₄. It was then filtered and evaporated *in vacuo* to afford bromide compound 1B as a dense yellow solid. ¹H NMR (CDCl₃, d = 7.281 ppm; 500 MHz): 8.03 (s, 1H), 5.61 (br s, 1H), 4.08 (br m, 1H), 3.66 (ddd, J = 13.9, 6.5, 3.2, 1H) 3.34 (ddd, J = 13.9, 7.9, 5.2, 1H), 2.23 (br s, 1H), 1.29 (d, J = 6.3, 3H). (ESI) m/z (M+H)⁺ = 267.94.

Step C:



DMSO (30 mL, 0.4228 mol) was added dropwise over 30 min. to a cooled (-78°C) CH₂Cl₂ (250 mL) solution of oxalyl chloride (20.3 mL, 0.2327 mol). The reaction mixture was stirred for 70 min, and then a CH₂Cl₂ (275 + 25 mL) solution of the crude alcohol from step B was added to it over 70 min. and stirring continued at -78°C. Half an hour later, TEA (60.0 mL) was added over 10 min, and then half an hour later, the cold bath was removed and the reaction mixture was allowed to thaw to rt over the next hour. The reaction mixture was washed with water (3x) and brine, dried (MgSO₄), 5 filtered, and evaporated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (CHCl₃) to afford ketone 1C as a yellow solid (26.18 g, a three step combined yield of 78.8 %). ¹H NMR (CDCl₃, δ = 7.26 ppm; 500 MHz): 8.02 (s, 1H), 5.97 (br s, 1H), 4.29 (d, J = 4.7, 2H), 2.28 (s, 3H). (ESI) m/z (M+H)⁺ = 265.98.

10

15

Step D:

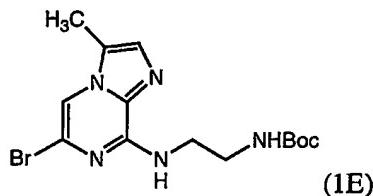


Trifluoroacetic anhydride (40.0 ml, 0.2832 mole) was added dropwise over 30 20 min. to a stirred trifluoroacetic acid (65.0 ml) solution of ketone 1C from step C (26.18 g, 0.0990 mole). The reaction mixture was stirred for 2.25 h and the volatile component was removed *in vacuo*. The resulting crude oil was dissolved in CHCl₃ and washed with a sufficient amount of sat'd NaHCO₃ that the wash had a slightly basic pH. The organic phase was washed with brine, dried (MgSO₄), filtered, and evaporated *in vacuo*. A silica

gel mesh of the crude material was prepared and submitted to flash chromatography (50 % EtOAc/hexanes) to afford imidazopyrazine 1D as an off-white fluffy solid (22.60 g, 92.6 %). ^1H NMR (CDCl_3 , δ = 7.26 ppm; 500 MHz): 8.00 (s, 1H), 7.65 (s, 1H), 2.53 (s, 3H). (ESI) m/z (M+H) $^+$ = 247.91.

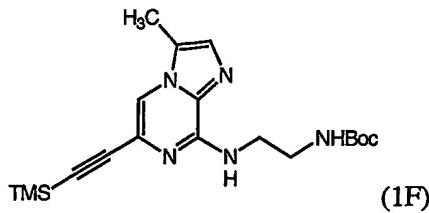
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Step E:



Imidazopyrazine 1D (8.23 g, 33.3888 mmol) was added to a THF (60.0 mL) solution of *tert*-butyl *N*-(2-aminoethyl)carbamate (6.20 g, 38.6968 mmol) and TEA (9.0 mL, 64.5716 mmol). The reaction mixture was heated with an oil bath (~ 65 °C) for 17 h, cooled to rt, and the precipitate filtered. Silica gel was added to the filtrate and evaporated *in vacuo*. The resulting silica gel mesh was submitted to flash chromatography (50-70 % EtOAc/hexanes) to afford bromide 1E as an off-white solid (11.149 g, 90.2 % yield). ^1H NMR (CDCl_3 , δ = 7.26 ppm; 500 MHz): 7.37 (s, 1H), 7.24 (s, 1H), 6.37 (br s, 1H), 5.13 (br s, 1H), 3.73 (app q, J = 5.7, 2H), 3.44 (m, 2H), 2.4 (d, J = 0.7, 3H), 1.43 (s, 9H). (ESI) m/z (M+H) $^+$ = 369.96/371.96.

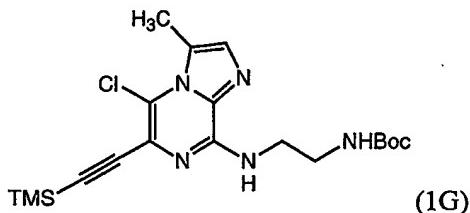
20 Step F:



A mixture of $\text{Pd}(\text{Ph}_3\text{P})_4$ (2.9180 g, 2.525 mmol) and CuI (0.8034g, 2.204 mmol) was added to a pressure tube containing a DMF (200 mL) solution of bromide 1E (22.67 g, 61.229 mmol), (trimethylsilyl)acetylene (20.0 mL, 0.1415 mol), and TEA (36.0 mL, 0.2582 mol). The reaction flask was flushed with nitrogen, capped, and heated at 64°C for ~ 16 h. The reaction mixture was then allowed to cool to rt and the precipitate was filtered. The filtrate was exposed to vacuum to remove the DMF and other volatile components. A silica gel mesh was prepared from the residue and submitted to flash chromatography (50-60 % EtOAc/hexanes) to afford alkyne 1F as a yellow foam (23.90 g). ^1H NMR (CDCl_3 , δ = 7.26 ppm; 500 MHz): 7.50 (s, 1H), 7.26 (s, 1H), 6.22 (app br s, 1H), 5.09 (app br s, 1H), 3.76 (app q, J = 5.8, 2H), 3.45 (m, 2H), 2.41 (s, 3H), 1.42 (s, 9H), 0.28 (s, 9H). (ESI) m/z ($M+\text{H}$)⁺ = 388.1.

Step G:

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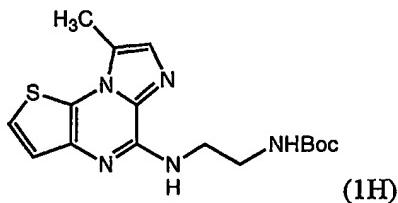


N-Chlorosuccinimide (9.1477 g, 68.51 mmol) was added to a THF (200 mL) solution of alkyne 1F (23.90g, 61.67 mmol), and the resulting reaction mixture was heated with an oil bath (~ 64°C) for 6 h. The solvent was removed *in vacuo*, and the residue was dissolved in CH_2Cl_2 and washed with water (2x) and brine. The organic layer was dried (MgSO_4), filtered, and evaporated *in vacuo*. The crude material was submitted to flash chromatography (the sample was loaded onto column with the eluting solvent; 30-40 % EtOAc/hexanes) to afford a clean chloride 1G and some impure fraction. The impure fraction was further purified as above to retrieve more pure material. Chloride 1G was obtained as a light yellow solid (20.07 g, a two step combined yield of 77.7 %). ^1H NMR: 7.61 (br t, J = 5.7, 1H), 7.35 (d, J = 0.7, 1H), 6.93 (br t, J = 5.4, 1H), 3.45 (app q, J

= 5.9, 2H), 3.17 (app q, J = 5.9, 2H), 2.69 (s, 3H), 1.36 (s, 9H), 0.25 (s, 9H). (ESI) m/z (M+H)⁺ = 422.24.

Step H:

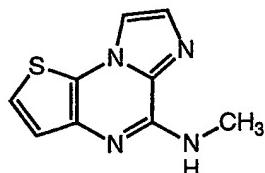
5



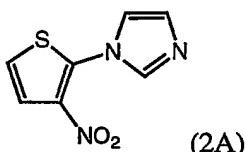
DMF (54.0 mL) was added to a mixture of chloroalkyne 1G (3.1377 g, 7.4353 mmol) and Na₂S·9H₂O (5.48 g, 22.82 mmol; the solid was crushed with mortar and pestle; 99.99 % pure). The resulting heterogeneous reaction mixture was heated for 65 min. with an oil bath pre-equilibrated at 100°C. The reaction mixture was allowed to cool to rt and the volatile component removed *in vacuo*. A silica gel mesh of the residue was prepared and submitted to flash chromatography (50 % EtOAc/hexanes) to afford amine 1H as a light yellow solid (1.46 g, ~ 56 %). ¹H NMR: 7.52 (d, J = 5.5, 1H), 7.36 (d, J = 0.9, 1H), 7.33 (br t, J = 5.7, 1H), 7.25 (d, J = 5.5, 1H), 6.96 (br t, J = 5.1, 1H), 3.53 (app q, J = 6.1, 2H), 3.22 (app q, J = 6.0, 2H), 2.69 (d, J = 0.8, 3H), 1.36 (s, 9H). (ESI) m/z (M+H)⁺ = 348.05.

Step I: Example 1

The Boc-protected compound 1H was deprotected by treatment with 20 % TFA/CH₂Cl₂ and stirring of the reaction mixture at rt for 0.5-1.0 hr. The volatile component was removed *in vacuo*, and the residue was treated with MeOH and rotavaped twice to remove most of the TFA. The resulting crude material was dissolved in either MeOH and/or DMF and purified on a PREP-HPLC to afford the TFA salt of Example 1. (ESI) m/z (M+H)⁺ = 248.27.

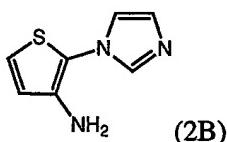
Example 2

Step A:



DMF (40 mL) was added into a flask containing imidazole (2.891 g, 42.4647 mmol) and 1-chloro-2-nitro-thiophene (2.9047 g, 17.7571 mmol), and the reaction mixture was heated at 90°C for 13.5 h. It was allowed to cool to rt and filtered, and the solvent was removed *in vacuo*. The resulting crude material was partitioned between EtOAc and water. The organic layer was washed with brine, dried (MgSO₄), filtered, and evaporated *in vacuo*. A silica gel mesh of the residue was prepared and submitted to flash chromatography (75-90 % EtOAc/hexanes) to afford the coupled material (2A) as a dull-yellow crystal (2.46 g, 71.0 %). ¹H NMR (CDCl₃, δ = 7.26 ppm; 500 MHz): 7.86 (s, 1H), 7.65 (d, J = 6.2, 1H), 7.28 (d, J = 6.3, 1H), 7.27 (1H, overlapped signal), 7.22 (m, 1H). (ESI) m/z (M+H)⁺ = 196.03.

Step B:

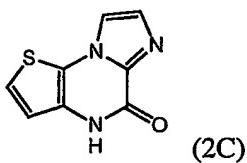


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MeOH (80 mL) was added into a hydrogenation apparatus that contained nitrothiophene 2A (2.32 g, 11.885 mmol), 10 % Pd/C (930 mg), and hydrogenated at 40

PSI. The reaction was allowed to proceed for a total of 22.25 h, the catalyst was filtered, and the filtrate rotovaped. The resulting crude oil was submitted to flash chromatography (0-5 % MeOH/EtOAc) to afford amine 2B as a dark-yellow oil that slowly crystallized to a waxy solid (1.72 g, 87.6 %). ^1H NMR (CDCl_3 , δ = 7.26 ppm; 500 MHz): 7.65 (s, 1H), 7.20 (s, 1H), 7.09 (m, 1H), 7.07 (d, J = 5.9, 1H), 6.61 (d, J = 6.0, 1H). (ESI) m/z (M+H) $^+$ = 166.21.

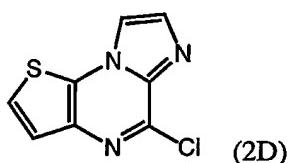
Step C:



10

o-Dichlorobenzene (30 mL) was added into a flask containing compound 2B (1.639 g, 9.9201 mmol) and 1,1'carbonyldiimidazole (1.961 g, 12.0937 mmol). The heterogeneous reaction mixture was heated at 140°C for 5.75 h and then allowed to cool to rt. It was diluted with ether (150 mL), and the solid was filtered and washed with copious ether. The brown solid was transferred into a flask containing EtOAc (20 mL), stirred for 15 min, filtered, and washed with EtOAc (20 mL). The solid was then transferred into a flask containing water (10 mL), stirred for 10 min, filtered, and washed with copious water. The resulting solid was dried *in vacuo* to provide 1.35 g of cyclized material 2C. ^1H NMR: 12.06 (s, 1H), 8.16 (d, J = 1.1, 1H), 7.56 (s, 1H), 7.51 (d, J = 5.7, 1H), 6.97 (d, J = 5.7, 1H) (ESI) m/z (M+H) $^+$ = 192.01.

Step D:



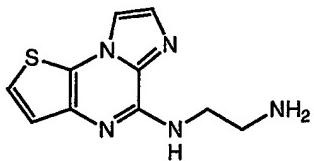
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N,N-Diethylaniline (2.0 mL, 12.57 mmol) and POCl₃ (20 mL) were added to the impure tricycle compound 2C (1.28 g), and the reaction mixture was refluxed for 6 h. After it was allowed to cool to rt, most of the volatile POCl₃ was removed *in vacuo*. The residue was partitioned between EtOAc and water. The aqueous layer was neutralized with solid Na₂CO₃, and an EtOAc extraction was done. The combined organic phase was washed with brine, dried (MgSO₄), filtered, and evaporated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (40-50 % EtOAc/hexanes) to afford chloride 2D as a white solid (0.8593 g, a two-step combined yield of 43.6 %). ¹H NMR (CDCl₃, δ = 7.26 ppm; 500 MHz): 7.93 (d, J = 0.85, 1H), 7.86 (s, 1H), 7.51 (d, J = 5.7, 1H), 7.37 (d, J = 5.7, 1H).

Step E: Example 2

Excess methylamine (2.0 mL, 40 % wt /H₂O) was added to a THF (3.0 mL) suspension of compound 2D (74.2 mg, 0.3539 mmol). The reaction mixture was stirred at rt for 13.75 h and at 60°C for 1.75 h, and the volatile component was removed *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (40 % EtOAc/hexanes) to afford Example 2 as a white fluffy solid (56 mg, 77.5 %). ¹H NMR (CDCl₃, δ = 7.26 ppm; 500 MHz): 7.60 (s, 1H), 7.58 (s, 1H), 7.32 (d, J = 5.6, 1H), 7.16 (d, J = 5.5, 1H), 6.09 (br s, 1H), 3.22 (d, J = 5.1, 3H). (ESI) m/z 20 (M+H)⁺ = 205.05.

Example 3

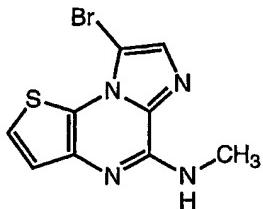


25

Excess ethylenediamine (5.0 mL) was added to chloride 2D (74 mg, 0.353 mmol), and the resulting reaction mixture was stirred at rt for 27 h. Most of the ethylenediamine

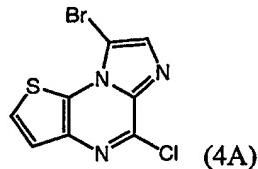
was removed *in vacuo*, and the residue was partitioned between EtOAc and sat'd NaHCO₃ solution. The aqueous layer was saturated with NaCl, and additional EtOAc extractions were conducted until no more product was removed as determined by TLC. The combined organic layer was directly submitted to flash chromatography (MeOH) to afford a viscous oil that ultimately crystallized into a white solid (59.6 mg, 72%). ¹H NMR: 8.18 (s, 1H), 7.62 (s, 1H), 7.48 (d, J = 5.7, 1H), 7.34 (br t, J = 5.6, 1H), 7.24 (d, J = 5.7, 1H), 3.48 (m, 2H), 2.80 (app t, J = 6.5, 2H). (ESI) m/z (M+H)⁺ = 234.02.

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Example 4

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Step A:

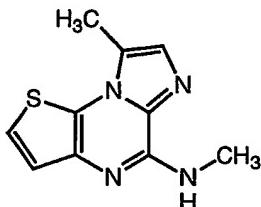


N-Bromosuccinimide (134.0 mg, 0.7529 mmol) was added in batches over a few minutes to a cooled (0°C) THF (4.5 mL) solution of compound 2D (152.5 mg, 0.7274 mmol), and the reaction mixture was stirred for 2.25 h. Silica gel was added into the reaction mixture, and the solvent was removed *in vacuo*. The resulting silica gel mesh was submitted to flash chromatography (15-20 % EtOAc/hexanes) to afford bromide 4A as a fluffy white solid (196.4 mg, 93.6 %). ¹H NMR (CDCl₃, δ = 7.26 ppm; 500 MHz): 7.83 (s, 1H), 7.53 (d, J = 5.7, 1H), 7.44 (d, J = 5.7, 1H). (ESI) m/z (M+H)⁺ = 287.83 / 289.83.

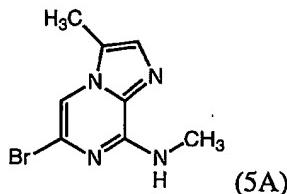
Step B: Example 4

Excess methylamine (2.0 mL, 40 % wt /H₂O) was added to a THF (3.0 mL) suspension of chloride 4A (105 mg, 0.3639 mmol). The reaction mixture was stirred at rt for 16.25 h, and the volatile component was removed *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (40 % EtOAc/hexanes) to afford Example 4 as a white fluffy solid (94.2 mg, 91.4 %). ¹H NMR: 7.71 (s, 1H), 7.59 (m, 1H), 7.56 (d, J = 5.6, 1H), 7.29 (d, J = 5.7, 1H), 2.97 (d, J = 4.9, 3H). (ESI) m/z (M+H)⁺ = 282.90/284.90.

10

Example 5

Step A:



15

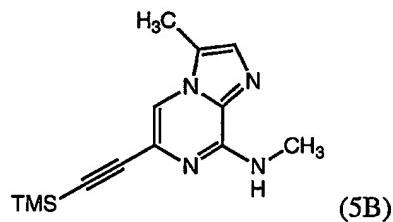
(5A)

Methylamine (30.0 mL, 40 % wt in water) was added to a THF (100 mL) solution of chloride 1D (21.65 g, 87.8331 mmol) in a pressure tube. A heavy suspension appeared in 10 min. The reaction mixture was stirred at rt for 5.5 h and then stored in a refrigerator for an additional 20 h. The precipitate was filtered, and the solid was washed with copious water and dried under vacuum to afford amine 5A as an off-white solid (17.6 g). The filtrate afforded a second crop when stored at rt for a few h (3.36 g off-white solid, a

combined yield of >98 %). ^1H NMR: 7.85 (m, 1H), 7.78 (s, 1H), 7.27 (d, J = 0.7, 1H), 2.91 (d, J = 4.9, 3H), 2.38 (d, J = 0.9, 3H). (ESI) m/z (M+H) $^+$ = (241.11/243.11).

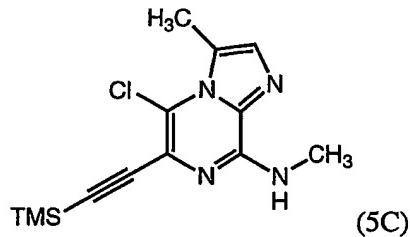
Step B:

5



Bromide 5A (17.60 g, 73.00 mmol) was converted to alkyne 5B following the procedure of Example 1, Step F, except: (a) 30 % less catalyst and co-catalyst were employed; and (b) the column was eluted with 40-60 % EtOAc/hexanes. Amine 5B was retrieved as a yellow solid (17.88 g). ^1H NMR 7.85 (s, 1H), 7.56 (m, 1H), 7.29 (d, J = 0.6, 1H), 2.92 (d, J = 4.9, 3H), 2.40 (s, 3H), 0.25 (s, 9H). (ESI) m/z (M+H) $^+$ = 259.42.

15 Step C:



N-Chlorosuccinimide (10.4825 g, 78.50 mmol) was added to a THF (200 mL) solution of compound 5B (17.88 g, 69.20 mmol), and the resulting reaction mixture was heated with an oil bath (~ 60°C) for 14 h. It was allowed to cool to rt, and the solvent was removed *in vacuo*. The residue was dissolved in CHCl₃ (350 mL), washed with water (150 mL, 3X) and brine, and the organic layer was evaporated *in vacuo*. A silica gel

mesh was prepared from the crude material and submitted to flash chromatography (30 % EtOAc/hexanes, until all the higher R_f impurities were eluted, then 50 % EtOAc/hexanes) to afford chloride 5C as an off-white solid (16.52 g, a two-step combined yield of 77.3 %). ¹H NMR: 7.66 (m, 1H), 7.33 (d, J = 0.9, 1H), 2.89 (d, J = 4.9, 3H), 2.69 (d, J = 1.0, 5 3H), 0.26 (s, 9H). (ESI) m/z (M+H)⁺ = 293.27.

Step D: Example 5

A stirred suspension of chloroalkyne 5C (17.68 g, 60.37 mmol) in DMF (310 mL, bubbled with argon) was treated with grounded sodium sulfide nonahydrate (43.5 g, 10 181.12 mmol, 99.99 % purity) at rt. After 5 min, LC/MS analysis of the reaction mixture showed complete desilylation. The mixture was then heated at 80°C for ~1 hr and the solvent evaporated *in vacuo*. The residue was dissolved in chloroform and washed with water. The aqueous phase was extracted with chloroform (3x) and the combined organic phase was dried (MgSO₄), filtered, and concentrated. The residue was submitted to flash 15 chromatography (50-100 % CH₂Cl₂/EtOAc) to afford Example 5 as a yellowish solid (8.35 g, 63.4 %).

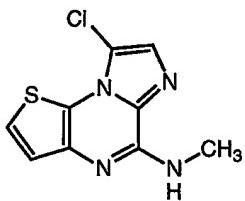
Alternate Process to Prepare Example 5:

Alternatively to Steps A-D, Example 5 was prepared from Example 4 as follows: 20 Tetramethyltin (2.4 mL, 17.326 mmol) was added into a DMF (19.0 mL) suspension of Example 4 (704 mg, 2.4863 mmol), PdCl₂(Ph₃P)₂ (185.1 mg, 0.2637 mmol) and KF (311 mg, 5.3528 mmol). After nitrogen was bubbled through the heterogeneous mixture for 30 seconds, it was heated at 90°C for 13.75 h. It was allowed to cool to rt and the volatile component was removed *in vacuo*. A silica gel mesh of the crude material was prepared 25 and submitted to flash chromatography (50 % EtOAc/hexanes) to afford a mixture of Example 5 and Ph₃PO in a 10:1 molar ratio (¹H NMR) (351 mg). A portion of the impure product was purified further on a PREP-HPLC, and the resulting TFA salt of Example 5 was converted to the free base: the salt was dissolved in water; the aqueous medium was basified with NaHCO₃ solution and extracted with EtOAc; the organic layer 30 was dried over MgSO₄ and the solvent was removed *in vacuo*. ¹H NMR: 7.51 (d, J = 5.5,

1H), 7.39 (m, 1H), 7.34 (d, J = 0.9, 1H), 7.27 (d, J = 5.6, 1H), 2.96 (d, J = 4.8, 3H), 2.69 (d, J = 0.8, 3H). (ESI) m/z (M+H)⁺ = 218.98.

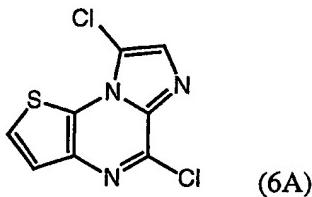
Example 6

5



Step A:

10



(6A)

N-Chlorosuccinimide (103.4 mg, 0.7744 mmol) was added to a THF (4.0 mL) solution of compound 3D (150.9 mg, 0.7198 mmol), and the reaction mixture was stirred at rt for 16 h. Silica gel was added to the mixture, and the solvent was removed *in vacuo*.

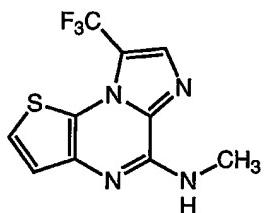
- 15 The resulting silica gel mesh was submitted to flash chromatography (20-30 % EtOAc/hexanes) to afford dichloride 6A as a white fluffy solid (157.4 mg, 89.6 %). ¹H NMR (CDCl₃, δ= 7.26 ppm; 500 MHz): 7.78 (s, 1H), 7.54 (d, J = 5.5, 1H), 7.47 (d, J = 5.8, 1H).

20 Step B: Example 6

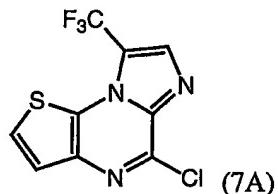
THF (3.0 mL) and methylamine (3.0 ml of 2.0M/THF) were added into a pressure tube containing dichloride 6A (51.3 g, 0.2102 mmol), and the reaction mixture was heated at 70°C for 3.25 h. It was transferred to a flask containing NaHCO₃ (29 mg) and a

few drops of water, shaken briefly, and the volatile component was removed *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (25-30 % EtOAc/hexanes) to afford Example 6 as a white solid (41.5 mg, 82.7 %). ¹H NMR: 7.71 (s, 1H), 7.63 (m, 1H), 7.59 (d, J = 5.7, 1H), 7.30 (d, J = 5.6, 1H), 2.98 (d, J = 4.6, 3H). (ESI) m/z (M+H)⁺ = 238.88.

Example 7



10 Step A:



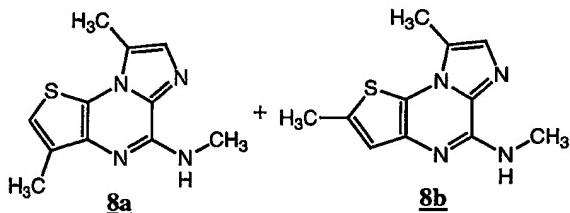
FO₂SCF₂CO₂Me (70 uL, 0.550 mmol) was added into a DMF (2.0 mL) suspension of compound 4A (156 mg, 0.5406 mmol) and CuI (13.1 mg, 0.0688 mmol). The reaction mixture was heated at 80°C for 4.25 h, FO₂SCF₂CO₂Me (70 uL) was added, it was heated for 4 more h, additional FO₂SCF₂CO₂Me (100 uL) was added, and it was heated for a final 23 h. Heating was stopped and the volatile component was removed *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (15 % EtOAc/hexanes) to afford compound 7A as a white solid (17 mg). ¹H NMR (CDCl₃, δ= 2.50 ppm; 500 MHz): 8.21 (s, 1H), 7.57 (d, J = 5.8, 1H), 7.52 (d, J = 5.8, 1H). (ESI) m/z (M+H)⁺ = 277.91.

Step B: Example 7

Methylamine (0.5 mL of 2.0 M/THF) was added into a THF (1.0 mL) solution of chloride 7A prepared above, and the reaction mixture was stirred at rt for 15.5 h. It was partitioned between EtOAc and 50 % sat'd NaHCO₃ solution. The organic layer was washed with brine, dried (MgSO₄), filtered, and evaporated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (20 % EtOAc/hexanes) to afford impure Example 7. It was purified on a PREP-HPLC, and the resulting TFA salt was converted to the free base as described in Example 5. Pure Example 7 was obtained as a white solid (9.8 mg, a combined yield of 6.7 %). ¹H NMR (CDCl₃, δ = 7.26 ppm; 500 MHz): 7.89 (s, 1H), 7.33 (d, J = 5.7, 1H), 7.29 (d, J = 5.8, 1H), 6.09 (br s, 1H), 3.22 (d, J = 5.1, 3H). (ESI) m/z (M+H)⁺ = 272.97.

Examples 8a and 8b

15



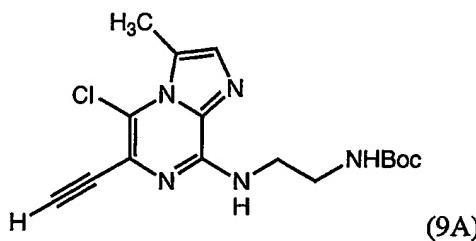
Butyllithium (500 uL of 1.6 M/hexanes, 0.80 mmol) was added over 2 min. to a cooled (-78°C) THF (3.0 mL) solution of Example 5 (81.0 mg, 0.3712 mmol), and the reaction mixture was stirred for 33 min. Iodomethane (50 uL, 0.8032 mmol) was added dropwise over 2 min, and stirring was continued at -78°C for an additional 8.75 h. The reaction mixture was quenched with MeOH and partitioned between EtOAc and water. The organic layer was washed with brine, dried (MgSO₄), filtered, and evaporated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (35-50 % EtOAc/hexanes) to afford pure amine 8a and impure amine 8b. Amine 8b was purified on a PREP-HPLC, and the resulting TFA salt was converted to the free base as described for Example 5 to provide Examples 8a (18.1 mg, 21 %), and

8b (17.2 mg, 20 %). ^1H NMR of 8a: 7.37 (br q, $J = 4.5$, 1H), 7.34 (d, $J = 0.85$, 1H), 7.17 (d, $J = 1.2$, 1H), 3.00 (d, $J = 4.8$, 3H), 2.68 (d, $J = 0.70$, 3H), 2.34 (d, $J = 1.1$, 3H). ^1H NMR of 8b : 7.34 (m, 1H), 7.31 (d, $J = 0.85$, 1H), 7.00 (d, $J = 1.3$, 1H), 2.94 (d, $J = 4.8$, 3H), 2.65 (d, $J = 0.7$, 3H), 2.53 (d, $J = 1.1$, 3H). For both samples, (ESI) m/z (M+H) $^+ =$

5 232.92.

Example 9

Step A:



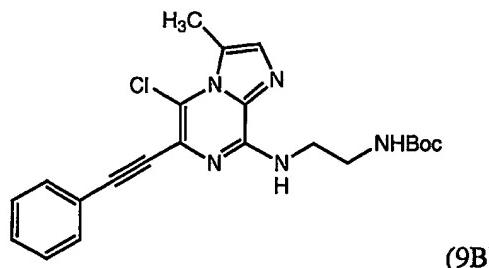
5

(9A)

K_2CO_3 (615 mg, 4.4498 mmol) was added to a MeOH (140 mL) solution of compound 1G (9.178 g, 21.7488 mmol), and the mixture was stirred for 46 min. The volatile component was removed *in vacuo* and the resulting residue was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried (MgSO_4), filtered, and evaporated *in vacuo*. Chloride 9A was obtained as a gray solid (7.51 g, 98.7 %). ^1H NMR: 7.64 (t, $J = 5.7$, 1H), 7.36 (d, $J = 0.6$, 1H), 6.93 (t, $J = 5.4$, 1H), 4.45 (s, 1H), 3.44 (app q, $J = 6.1$, 2H), 3.17 (app q, $J = 6.0$, 2H), 2.70 (d, $J = 0.6$, 3H), 1.36 (s, 9H). (ESI) m/z $(\text{M}+\text{H})^+ = 350.15$.

15

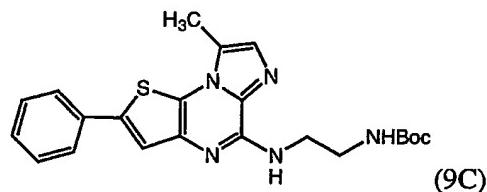
Step B:



A mixture of $\text{Pd}(\text{Ph}_3\text{P})_4$ (22.8 mg, 0.1973 mmol) and CuI (6.7 mg, 0.0352 mmol) was added to a DMF (2.0 mL) solution of alkyne 9A (70.8 mg, 0.2024 mmol), iodobenzene (196.8 mg, 0.9647 mmol), and TEA (150 μL , 1.076 mmol). The reaction mixture was stirred at rt for 15 h. The volatile components were removed *in vacuo*, and a 5 silica gel mesh of the residue was prepared and submitted to flash chromatography (35 % EtOAc/hexanes) to afford alkyne 9B as an off-white foam (71.6 mg, 83 %). ^1H NMR (CDCl_3 , δ = 7.26 ppm; 500 MHz): 7.62 (m, 2H), 7.37 (m, 3H), 7.22 (s, 1H), 6.25 (br s, 1H), 5.11 (br s, 1H), 3.75 (app q, J = 5.7, 2H), 3.45 (m, 2H), 2.78 (s, 3H), 1.42 (s, 9H). (ESI) m/z $(\text{M}+\text{H})^+$ = 426.17.

10

Step C:



DMF (2.0 mL) was added to a mixture of chloride 9B (70.3 mg, 0.1651 mmol) and $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ (239 mg, 0.995 mmol, 99.99 %). The heterogeneous mixture was heated for 45 min. at 100°C. The volatile component was removed *in vacuo*, and the residue was partitioned between EtOAc and 50 % sat'd NaCl solution. The organic layer was dried (MgSO_4), filtered, and evaporated *in vacuo*. A silica gel mesh was prepared from the crude material and submitted to flash chromatography (50-60 % EtOAc/hexanes) to 15 afford the cyclized Boc-protected product 9C as an orange foam (52 mg, 74 % yield). ^1H NMR (CDCl_3 , δ = 7.26 ppm; 500 MHz): 7.65 (m, 2H), 7.51 (s, 1H), 7.43 (m, 2H), 7.34 (m, 1H), 7.29 (s, 1H), 6.22 (br s, 1H), 5.39 (br s, 1H), 3.78 (app q, J = 5.7, 2H), 3.48 (m, 2H), 2.77 (s, 3H), 1.44 (s, 9H).

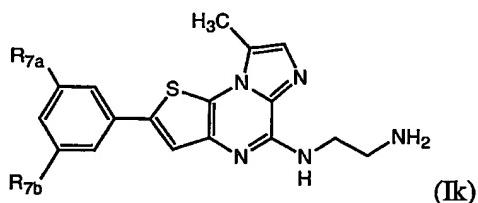
^{13}C -NMR (CDCl_3 , δ = 77.0 ppm; 125.7 MHz): 156.2, 147.8, 140.1, 136.7, 133.8, 25 132.5, 130.1, 129.1, 128.1, 125.5, 123.9, 119.5, 119.4, 79.3, 41.1, 41.0, 28.4, 10.4. Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_5\text{O}_2\text{S}$: C, 62.38; H, 5.94; N, 16.53. Found: C, 62.21; H, 5.89; N, 16.49. HRMS calcd for $(\text{M}+\text{H})^+$ 424.1807, found 424.1815.

Step D: Example 9

Amine 9C (52 mg, 0.1228 mmol) was treated with 25 % TFA/CH₂Cl₂ (4.0 mL), and the reaction mixture was stirred for 1.25 hr. The volatile component was removed *in vacuo*, and the residue was treated with 2 mL MeOH and 1.0 mL of 1.0 M NaOH/H₂O solution and rotovaped again. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (short column; MeOH) to afford the deprotected Example 9 as an off-white solid (29.3 mg, 76 %). (ESI) m/z (M+H)⁺ = 324.15.

A portion of the compound obtained above (24 mg, 0.0743 mmol) was dissolved in 2-propanol (9.0 mL) with mild heating, and the solution was filtered to remove particles. HCl (75 uL of 1.00 M/H₂O, 0.075 mmol) was added to the filtrate and the volatile component was removed *in vacuo* to afford the HCl salt of amine 9 as an off-white solid. ¹H NMR of HCl salt: 7.77 (d, J = 7.3, 2H), ~ 7.77 (br s, 3H, overlapped with the doublet, RNH₃⁺), 7.72 (s, 1H), 7.68 (app t, J = 5.7, 1H), 7.47 (app t, J = 7.7, 2H), 7.43 (s, 1H), 7.37 (app t, J = 7.5, 1H), 3.74 (app q, J = 5.8, 2H), 3.14 (app t, J = 6.1, 2H), 2.75 (s, 3H). HRMS calcd for (M+H)⁺ 324.1283, found 324.1287.

Alternatively, when clean compound 9C is submitted to the Boc deprotection protocol, removal of the volatile component affords a clean TFA salt. ¹H NMR: 7.81 (br s, 3H), 7.77 (m, 2H), 7.71 (s, 1H), 7.69 (t, J = 5.8, 1H), 7.47 (m, J = 7.8, 2H), 7.43 (d, J = 0.9, 1H), 7.37 (m, 1H), 3.75 (app q, J = 5.9, 2H), 3.16 (m, 2H), 2.76 (d, J = 1.0, 3H).

Examples 10-12

25

Compounds having the formula (Ik), above, wherein the R₇ substituents have the values listed in Table 1, were prepared following the procedure described in Example 9,

except instead of iodobenzene in step B, appropriately-substituted iodobenzene compounds were used (*e.g.*, P3 for Example 12). In Step D, MeOH may be used instead of 2-propanol for HCl salt formation. For Example 12, deprotection and purification was carried out as per Example 1, Step I.

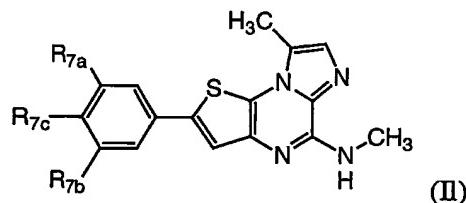
5

TABLE 1

EX. #	R _{7a}	R _{7b}	ESI (M+H) ⁺
10	-CH ₃	H	338.13
11	-CH ₃	-CH ₃	352.18
12	-OCH ₃	-OCH ₃	384.25

Examples 13-16

10



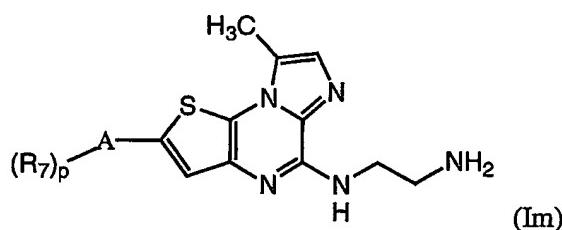
- Compounds having the formula (II) wherein the R₇ substituents have the values listed in Table 2, were prepared following the procedure described hereinafter for
- 15 Example 56, Step B, using appropriately-substituted iodobenzene compounds as the coupling components. For Examples 15 and 16, the crude material obtained from Step C was purified with a combination of flash chromatography and PREP HPLC, and the resultant TFA salt was converted to the free base as described for Example 5.

20

TABLE 2

EX. #	R _{7a}	R _{7c}	R _{7b}	(M+H) ⁺
-------	-----------------	-----------------	-----------------	--------------------

13	-CH ₃	H	H	309.13
14	H	-CH ₂ CH ₃	H	323.12
15	-CH ₃	H	-CH ₃	323.13
16	-CH ₃	-CH ₃	H	323.12

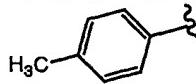
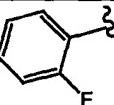
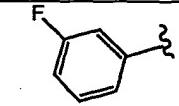
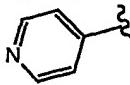
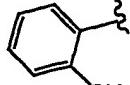
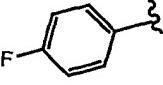
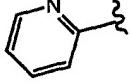
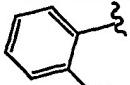
Examples 17-27

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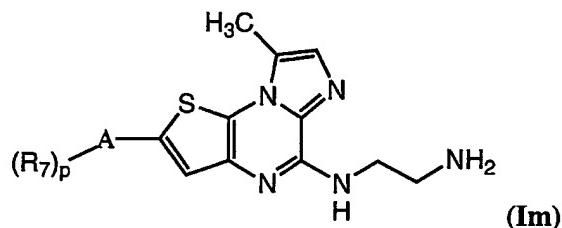
Compounds having the formula (Im), wherein A-(R₇)_p together have the values listed in Table 3, were prepared as described in Example 9, except in Step B, appropriately-substituted aryl or heteroaryl halides were used, and in Step C 10 (cyclization), the aqueous work-up step was omitted.

TABLE 3

Ex. #	A-(R ₇) _p	(M+H) ⁺	¹ H-NMR
17		354.08	
18		354.10	
19		325.13	

Ex. #	A-(R ₇) _p	(M+H) ⁺	¹ H-NMR
20		338.05	
21		342.06	
22		342.06	
23		325.06	8.70 (d, J = 6.4, 2H), 8.17 (s, 1H), 7.96 (d, J = 5.5, 2H), 7.81 (m, 4H), 7.47 (s, 1H), 3.75 (app q, J = 5.9, 2H), 3.16 (m, 2H), 2.77 (s, 3H).
24		354.05	
25		341.99	
26		325.02	
27		339.21	

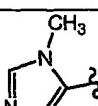
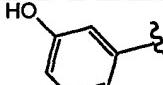
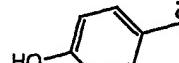
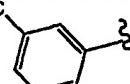
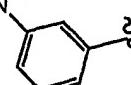
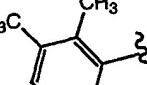
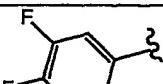
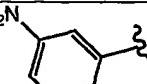
Examples 28-55

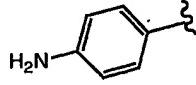
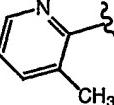
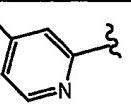
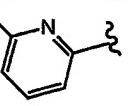
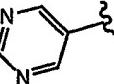
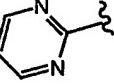
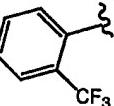
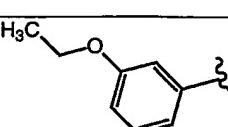


Compounds having the formula (Im), wherein A-(R₇)_p together have the values listed in Table 4, were prepared as described in Example 9, except in Step B (coupling), 5 appropriately-substituted halides were used in place of iodobenzene and the reaction mixture was heated at about 60°C until the chloroalkyne was completely consumed; in Step C (cyclization), the aqueous work-up step was omitted; and in Step D (deprotection), the deprotection procedure described in Example 1, Step I was used to produce the deprotected compounds as the TFA salt. For Example 55, P14 was used in 10 Step B and then the tosyl group was removed during the cyclization step.

TABLE 4

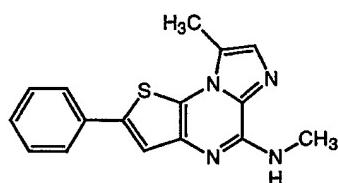
Ex. #	A-(R ₇) _p	(M+H) ⁺	¹ H-NMR
28		314.19	8.06 (br s, 2H), 7.79 (br s, 3H), 7.63 (br t, J = 5.7, 1H), 7.40 (d, J = 0.9, 1H), 7.37 (s, 1H), 3.73 (app q, J = 5.9, 2H), 3.14 (m 2H), 2.71 (d, J = 0.9, 3H).
29		331.13	7.87 (d, J = 3.3, 1H), 7.84 (s, 1H), 7.82 (d, J = 3.3, 1H), 7.79 (br t, J = 5.7, 1H), 7.85-7.80 (broad signal, 3H), 7.45 (d, J = 0.9, 1H),

Ex. #	A-(R ₇) _p	(M+H) ⁺	¹ H-NMR
			3.74 (app q, J = 5.8, 2H), 3.15 (m, 2H), 2.75 (s, 3H)
30		328.20	9.11 (s, 1H), 8.00 (s, 1H), 7.84 (br s, 3H), 7.81 (br t, J = 5.8, 1H), 7.69 (s, 1H), 7.46 (s, 1H), 3.95 (s, 3H), 3.74 (app q, J = 6.0, 2H), 3.15 (m, 2H), 2.72 (s, 3H).
31		340.19	
32		340.20	
33		392.15	
34		367.23	
35		352.21	
36		360.15	
37		339.16	7.83 (br s, 3H), 7.71 (br t, J = 5.7, 1H), 7.58 (s, 1H), 7.43 (d, J = 1.0, 1H), 7.22 (app t, J = 7.8, 1H), 7.14 (br

Ex. #	A-(R ₇) _p	(M+H) ⁺	¹ H-NMR
			d, J = 7.3, 1H), 7.08 (s, 1H), 6.75 (br d, J = 7.0, 1H), 3.74 (app q, J = 5.9, 2H), 3.15 (m, 2H), 2.75 (s, 3H)
38		339.19	
39		339.18	
40		339.18	
41		339.13	
42		326.12	9.24 (s, 2H), 9.16 (s, 1H), 7.97 (s, 1H), 7.83 (br s, 3H), 7.78 (br t, J = 5.8, 1H), 7.46 (d, J = 0.8, 1H), 3.75 (app q, J = 5.9, 2H), 3.16 (m, 2H), 2.76 (d, J = 0.6, 3H)
43		326.13	
44		392.14	
45		368.22	7.84 (br s, 3H), 7.74 (s, 1H), 7.69 (br t, J = 5.6, 1H), 7.43 (d, J = 0.9, 1H), 7.36 (app t, J = 7.9, 1H), 7.31-7.28 (m,

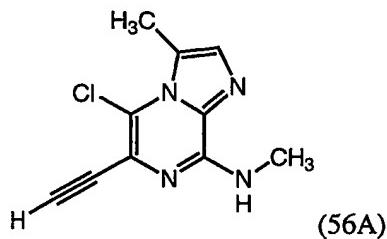
Ex. #	A-(R ₇) _p	(M+H) ⁺	¹ H-NMR
			2H), 6.93 (ddd, J = 8.2, 2.3, 0.7, 1H), 4.12 (q, J = 6.9, 2H), 3.74 (app q, J = 5.9, 2H), 3.16 (m, 2H), 2.75 (d, J = 0.6, 3H), 1.36 (t, J = 6.9, 3H)
46		382.24	
47		368.17	
48		340.12	8.36 (d, J = 2.1, 1H), 8.24 (d, J = 8.6, 1H), 7.82 (br s, 3H), 7.72 (br t, J = 5.7, 1H), 7.68 (s, 1H), 7.44 (d, J = 0.9, 1H), 6.99 (d, J = 9.2, 1H), 3.73 (app q, J = 5.8, 2H), 3.15 (m, 2H), 2.73 (s, 3H).
49		340.18	
50		355.20	
51		355.13	

Ex. #	A-(R ₇) _p	(M+H) ⁺	¹ H-NMR
52		328.34	
53		354.19	
54		355.14	
55		314.13	

Example 56

5

Step A:

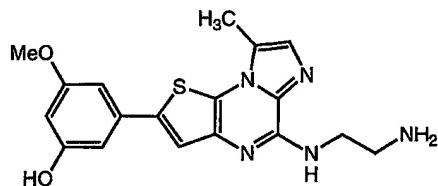


- Trimethylsilyl compound 5C was desilylated according to the procedure in
 10 Example 9, step A to afford chloroalkyne 56A. ¹H NMR: 7.69 (m, 1H), 7.34 (d, J = 0.9, 1H), 4.44 (s, 1H), 2.89 (d, J = 4.9, 3H), 2.69 (s, 3H). (ESI) m/z (M+H)⁺ = 221.13.

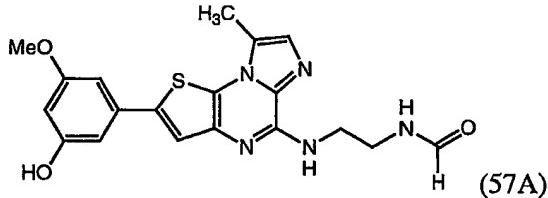
Step B:

The coupling procedure of Example 9, Step B, was followed, except the reaction mixture was heated at 60°C until the chloroalkyne was completely consumed. The resulting phenylalkynyl compound was then cyclized following Example 9, Step C, to afford Example 56A above as a free-base. (ESI) m/z (M+H)⁺ = 295.12.

10

Example 57

15

Step A:

15

DMF (1.5 mL) was added into a mixture of the Boc-protected precursor of Example 12 (50.8 mg, 0.1050 mmol) and NaSMe (52.3 mg, 0.7461 mg). The reaction mixture was lowered into a 100°C oil bath, and within minutes a heavy suspension was formed. The heterogeneous mixture was stirred at 100°C for 16 h. LC/MS of the crude reaction mixture indicated the presence of amine 57A. To ensure removal of the Boc group and quench the NaSMe, DMF was removed *in vacuo* and the residue was treated with 20% TFA/CH₂Cl₂ (2.5 mL) for 30 min. The volatile component was removed *in*

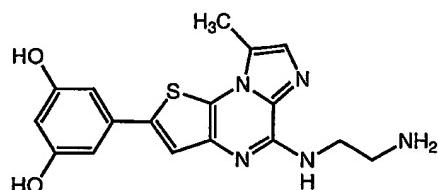
vacuo and the residue azeotroped with MeOH (2X). The crude material was dissolved in MeOH and submitted to PREP-HPLC purification to afford the TFA salt of amine 57A.

Step B: **Example 57**

5 The TFA salt of compound 57A was treated with hydrazine (2.0 mL), and stirred at 100°C for 4.5 h. The hydrazine was removed *in vacuo* and the residue dissolved in MeOH/H₂O (2:1) and purified on PREP HPLC to afford the TFA salt of Example 57 as an off-white solid (10.7 mg). (ESI) m/z (M+H)⁺= 370.18.

10

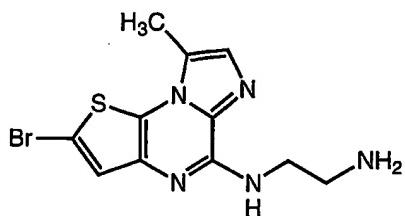
Example 58



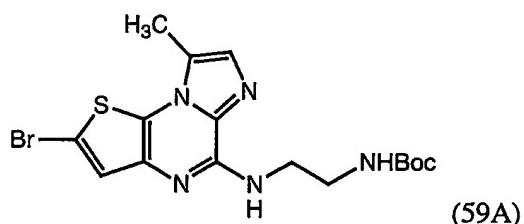
BBr₃ (1.5 mL of 1.0 M/CH₂Cl₂) was added dropwise over 3 min. to a cooled (-25°C) CH₂Cl₂ (2.0 mL) solution of Boc-protected precursor of Example 12 (125 mg, 0.2585 mmol). A yellow suspension appeared after the first drop of BBr₃ was added. The heterogeneous reaction mixture was stirred for 5.5 h while allowing the bath to thaw to ~0°C. The bath was removed and the side of the reaction flask was washed with CH₂Cl₂ (3.0 mL). The reaction mixture was stirred for an additional 1 hr, then quenched with MeOH and the solvent removed *in vacuo*. The crude material was dissolved in water and purified on a PREP-HPLC to afford the TFA salt of Example 58 as an off-white solid (77 mg). (ESI) m/z (M+H)⁺= 356.17.

Example 59

25



Step A:



5

N-Bromosuccinimide (1.42 g, 7.9780 mmol) was added in batches over 5 min to a cooled (ice-water) THF (47.0 mL) suspension of amine from Example 1, Step H (2.59 g, 7.4545 mmol). The reaction mixture was stirred for 17 h while allowing the bath to thaw. After removing the solvent *in vacuo*, the resultant solid residue was dissolved in CHCl₃ (300 mL; pre-washed with NaHCO₃ solution) and washed with water (150 mL, 3X) and brine. It was dried (MgSO₄), filtered, and evaporated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (50-70 % EtOAc/hexanes) to afford bromide 59A as an off-white fluffy solid (2.7570 g, 86.8 % yield). ¹H NMR: 7.49 (br t, J = 5.8, 1H), 7.46 (s, 1H), 7.36 (d, J = 0.8, 1H), 6.96 (br t, J = 5.4, 1H), 3.52 (app q, J = 6.0, 2H), 3.21 (app q, J = 5.9, 2H), 2.64 (s, 3H), 1.36 (s, 9H). (ESI) m/z (M+H)⁺ = 425.90/427.90. HRMS calcd for (M+H)⁺ 426.0599, found 426.0599.

Step B:

Compound 59A was deprotected following the procedure described in Example 1, Step I. The residue obtained after the removal of the volatile components was taken up in water and washed with EtOAc. The aqueous layer was evaporated to dryness. The resultant crude material was dissolved in MeOH and submitted to PREP-HPLC to afford the TFA salt of Example 59. ¹H NMR: 7.81 (br s, 3H), 7.74 (br t, J = 5.8, 1H), 7.46 (s,

1H), 7.41 (d, J = 0.9, 1H), 3.71 (app q, J = 6.0, 2H), 3.12 (m, 2H), 2.65 (d, J = 0.6, 3H).
 (ESI) m/z (M+H)⁺ = 327.7.

Examples 60-68

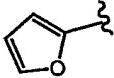
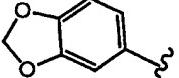
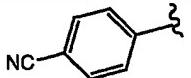
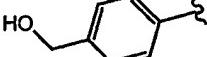
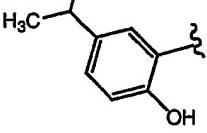
5

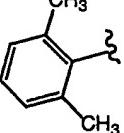
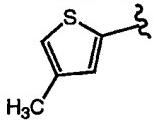
To prepare compounds having the formula (Im), above (as in Examples 28-55) wherein A-(R₇)_p together have the values listed in Table 5, below, 1.0 mL each of MeOH, toluene, and sat'd NaHCO₃ solution were added into a pressure tube containing bromide 59A (99.9 mg, 0.2343 mmol), (R₇)_pA-B(OH)₂ (1.5-1.8 mol equiv.) and Pd(Ph₃P)₄ (10.2 mg, 0.0087 mmol). Nitrogen was bubbled through the biphasic reaction mixture for a few minutes, and it was heated at 80°C for at least 9 h. When bromide 59A was totally consumed, the reaction mixture was cooled to rt and partitioned between brine and EtOAc. The organic layer was dried (MgSO₄), filtered and evaporated *in vacuo*. A silica gel mesh was prepared from the crude material and submitted to flash chromatography to afford compound of Examples 60-68 wherein the ethylamine side chain was Boc-protected. Deprotection following the procedure of Example 59, step B afforded Examples 60-68 as the TFA salt. At times, the crude material obtained after the work-up step of the deprotection procedure could be purified via trituration from MeOH.

20

TABLE 5

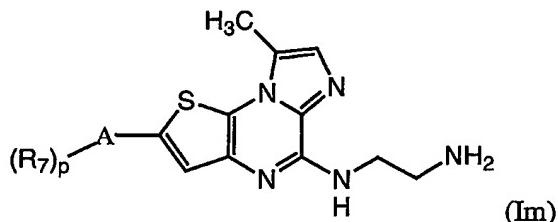
Ex. #	A-(R ₇) _p	(M+H) ⁺	Other Data (¹ H NMR)
60		354.0	(TFA salt): 7.84 (br s, 3H), 7.71-7.66 (m, 4H), 7.44-7.41 (m, 2H), 7.31 (d, J = 7.6, 1H), 4.57 (s, 2H), 3.75 (app q, J = 5.8, 2H), 3.16 (m, 2H), 2.76 (d, J = 0.6, 3H).
61		349.1	(TFA salt): 8.28 (app t, J = 1.6, 1H), 8.08 (ddd, J = 8.1, 1.9, 1.2, 1H), 7.93 (br s, 3H), 7.90 (s, 1H),

Ex. #	A-(R ₇) _p	(M+H) ⁺	Other Data (¹ H NMR)
			7.80 (dd, J = 7.9, 1.2, 1H), 7.73 (br t, J = 5.7, 1H), 7.66 (app t, J = 7.9, 1H), 7.44 (d, J = 0.9, 1H), 3.75 (app q, J = 5.9, 2H), 3.16 (m, 2H), 2.75 (d, J = 0.9, 3H)
62		314.0	(TFA salt): 7.82 (br s, 3H), 7.78 (dd, J = 1.8, 0.6, 1H), 7.71 (br t, J = 5.7, 1H), 7.50 (s, 1H), 7.43 (d, J = 0.9, 1H), 6.94 (d, J = 3.3, 1H), 6.66 (dd, J = 3.7, 1.9, 1H), 3.74 (app q, J = 6.0, 2H), 3.14 (m, 2H), 2.73 (d, J = 0.6, 3H).
63		368.1	(TFA salt): 7.85 (br s, 3H), 7.66 (br t, J = 5.7, 1H), 7.59 (s, 1H), 7.41 (d, J = 0.9, 1H), 7.40 (d, J = 1.8, 1H), 7.21 (dd, J = 8.1, 2.0, 1H), 7.00 (d, J = 8.0, 1H), 6.09 (s, 2H), 3.74 (app q, J = 5.9, 2H), 3.15 (m, 2H), 2.73 (d, J = 1.0, 3H)
64		349.1	
65		354.0	
66		382.1	

Ex. #	A-(R ₇) _p	(M+H) ⁺	Other Data (¹ H NMR)
67			(TFA salt): 7.83 (br s, 3H), 7.66 (br t, J = 5.8, 1H), 7.43 (d, J = 0.9, 1H), 7.27 (dd, J = 8.1, 7.2, 1H), 7.19 (d, J = 7.6, 2H), 7.09 (s, 1H), 3.75 (app q, J = 5.9, 2H), 3.15 (m, 2H), 2.69 (s, 3H), 2.19 (s, 6H)
68		344.0	

Examples 69-87

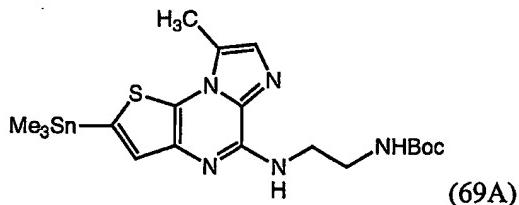
5



Compounds having the above formula (Im), wherein A-(R₇)_p together have the values listed in Table 6, were prepared following Steps A and B below.

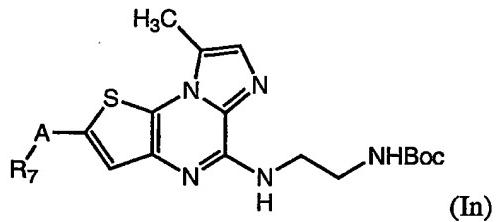
Step A:

10



A toluene (40 mL) solution of hexamethylditin (8.40g, 25.64 mmol) was treated with bromide 59A (3.00 g, 7.0 mmol) and TEA (1.96 mL, 14.06 mmol). After nitrogen was bubbled through the mixture for 5 min, Pd(Ph_3P)₄ (0.28 g, 0.24 mmol) was added. The reaction mixture was heated with a 100°C oil bath for 35 min. The dark reaction mixture was cooled to rt, filtered through a pad of Celite, washed with EtOAc, and the filtrate was evaporated *in vacuo*. The resulting oil was triturated with 5 % EtOAc/hexanes and the black precipitate removed by filtration. The filtrate was again evaporated to dryness, the residue treated with hexanes, heated to boiling and allowed to cool to rt. The side of the flask was scratched to induce crystallization and the solid allowed to stand at rt. The yellow/brown solid was collected by filtration, washed with hexanes, and allowed to air dry under vacuum to produce stannane 69A with traces of Ph₃PO and amine 1H as impurities (2.90 g, ~ 80 % yield). ¹H NMR: 7.33 (d, J = 0.6, 1H), 7.31-7.29 (m, 2H), 6.99 (br t, J = 5.2, 1H), 3.53 (app q, J = 6.0, 2H), 3.22 (app q, J = 5.9, 2H), 2.69 (s, 3H), 1.36 (s, 9H), 0.40 (s, 9H; 2 satellite peaks are observed with a J = 57.3, 15 60.2). (ESI) m/z (M+H)⁺ = 511.88.

Step B:



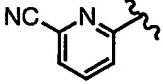
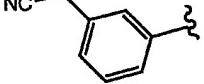
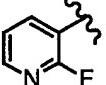
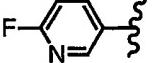
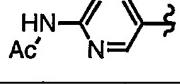
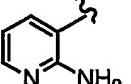
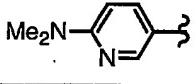
20 A mixture of PdCl₂(Ph₃P)₂ (10.9 mg, 0.0155 mmol) and CuI (4.0 mg, 0.0210 mmol) was added to a THF (2.0 mL) solution of stannane 69A (79.0 mg, ~ 0.1548 mmol) and appropriately-selected (R₇)_pA-Br or (R₇)_pA-I (2-3 mole equiv) (*see, e.g.*, Preparations 1-78 or commercially available sources). (A catalyst “pre-mix” could be prepared from PdCl₂(Ph₃P)₂ and CuI for multiple use by mixing and grinding together according to the indicated relative amounts). Nitrogen was bubbled through the solution for a few minutes, and the reaction mixture was lowered into a 70°C oil bath. After stannane 69A

was completely consumed, a silica gel mesh was prepared from the reaction mixture and submitted to standard flash chromatography protocol to afford the aryl-tricycle compound of formula (In), above. Also, the Stille product was contaminated with amine 1H and Ph₃PO to various degrees. The impure product was deprotected as described in Example 5 1, Step I, to provide Examples 69-87 as the TFA salt.

TABLE 6

Ex. #	A-(R ₇) _p	(M+H) ⁺	Other Data (¹ H NMR)
69		355.19	
70		340.20	(TFA salt): 10.55 (s, 1H), 7.82 (br s, 3H), 7.79 (dd, J = 8.0, 1.6, 1H), 7.77 (s, 1H), 7.63(br t, J = 5.5, 1H), 7.41 (d, J = 0.9, 1H), 7.18 (m, 1H), 6.99 (dd, J = 8.0, 1.0, 1H), 6.91 (m, 1H), 3.75 (app q, J = 5.8, 2H), 3.16 (m, 2H), 2.75 (s, 3H).
71		338.22	
72		341.03	
73		440.20	

Ex. #	A-(R ₇) _p	(M+H) ⁺	Other Data (¹ H NMR)
74		354.0	
75		349.0	
76		355.20	
77		355.18	(TFA salt): 8.29 (dd, J = 7.3, 1.8, 1H), 7.89 (s, 1H), 7.82 (dd, J = 6.6, 1.7, 1H), ~7.82 (br s, 3H, overlapping signal), 7.61 (br t, J = 5.6, 1H), 7.41 (d, J = 0.9, 1H), 6.48 (app t, J = 6.9, 1H), 3.74 (app q, J = 5.9, 2H), 3.60 (s, 3H), 3.16 (m, 2H), 2.77 (d, J = 0.6, 3H).
78		369.19	
79		313.9	(TFA salt): 8.22 (app t, J = 1.1, 1H), 7.81 (app t, J = 1.7, 1H), 7.79 (br s, 3H), 7.65 (br t, J = 5.7, 1H), 7.47 (s, 1H), 7.42 (d, J = 0.9, 1H), 6.98 (dd, J = 2.0, 0.8, 1H), 3.73 (app q, J = 5.9, 2H), 3.14 (m, 2H), 2.72 (d, J = 0.9, 3H)
80		350.18	(TFA salt): 9.28 (d, J = 2.4, 1H), 8.97 (d, J = 1.8, 1H), 8.74 (app t,

Ex. #	A-(R ₇) _p	(M+H) ⁺	Other Data (¹ H NMR)
			J = 2.1, 1H), 8.00 (s, 1 H), 7.82 (br s, 3H), 7.76 (br t, J = 5.7, 1H), 7.46 (d, J = 0.9, 1H), 3.75 (app q, J = 5.9, 2H), 3.16 (m, 2H), 2.76 (d, J = 0.6, 3H)
81		350.19	
82		362.9	(TFA salt): 7.81 (br s, 3H), 7.77 (br d, J = 7.6, 1H), 7.74 (s, 1H), 7.72-7.70 (m, 2H), 7.51 (app t, J = 7.8, 1H), 7.44 (d, J = 0.9, 1H), 7.36 (br d, J = 7.6, 1H), 4.12 (s, 2H), 3.75 (app q, J = 5.9, 2H), 3.16 (m, 2H), 2.76 (s, 3H)
83		343.17	
84		343.14	
85		382.16	
86		340.13	
87		368.12	

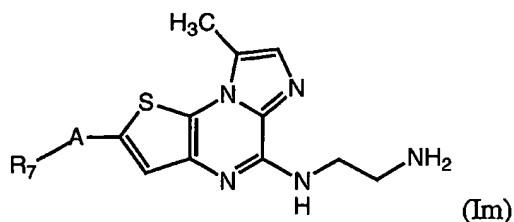
Example 88



Example 88 may be prepared by adding MeOH (2.0 mL) and NaOH (1mL of 1.0 M/H₂O) to the Boc-protected precursor of Example 73 (68 mg, 0.1260 mmol) and stirring 5 the heterogeneous reaction mixture at 75°C for 17 h. Since the deprotection was still not complete, MeOH (2.0 mL) and excess NaOH (244 mg, 6.10 mmol) were added and heating continued for an additional 3 h. The reaction mixture was neutralized with 1.0 N HCl, and the volatile component removed *in vacuo*. A silica gel mesh of the crude 10 material was prepared and submitted to flash chromatography (0-100 % MeOH/EtOAc) to afford the Boc-protected precursor of Example 88 (~30 mg, 54 %). Deprotection was carried out as described in Example 1, Step I, to afford Example 88. (ESI) m/z (M+H)⁺ = 341.11.

Examples 89-106

15



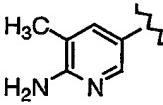
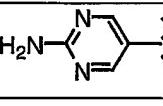
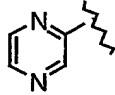
To prepare compounds having the formula (Im), above, wherein A-R₇ together have the values listed in Table 7, compound 69A (82.2 mg, ~ 0.1611 mmol), the coupling 20 partner ((R₇)_pA-Br or (R₇)_pA-I, 2-3 mol equiv)(*see, e.g.*, Preparations 1-78 or commercially available sources), PdCl₂(Ph₃P)₂ (0.0158 mmol), KF (19.4 mg, 0.3339 mmol) and DMF (2.0 mL) were sequentially added into a vial. Nitrogen was bubbled through the heterogeneous reaction mixture for about one minute, and it was lowered into

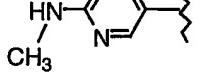
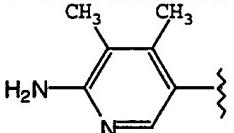
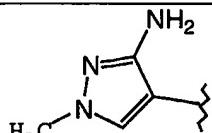
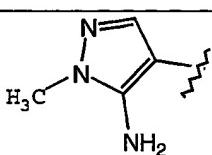
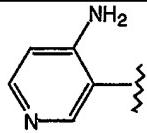
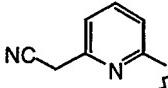
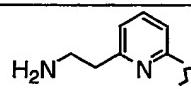
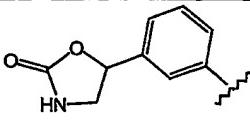
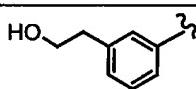
a 90°C oil bath and heated for at least 6 h. When the stannane 69A was completely consumed, the DMF was removed *in vacuo*, and a silica gel mesh was prepared from the resulting crude material and submitted to flash chromatography to afford the desired compound.

The Boc-protected amines were deprotected as set forth in Example 1, step I, to provide the TFA salt. The Boc-protected precursor of Example 100 was deprotected, however, following the procedure set forth above for Examples 60-68. Example 101 was made by reversing the stannane and halide groups on the coupling partners. For Examples 102 –106, an acylated phenol (*e.g.*, P10 or an analog thereof) was used as the coupling partner and the resulting product was deacylated using a known protocol (K₂CO₃/MeOH/water) and Boc-deprotected as in Example 59, step B, to achieve the desired compound.

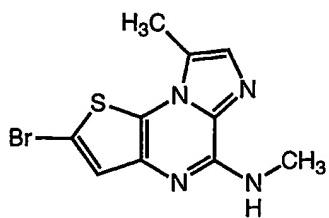
TABLE 7

15

Ex.	A-R ₇	(M+H) ⁺	¹ H NMR
89		354.10	
90		341.10	
91		326.11	(MeOH, δ = 3.31 ppm; TFA salt): 9.17 (d, J = 1.5, 1H), 8.56 (dd, J = 2.4, 1.5, 1H), 8.45 (d, J = 2.4, 1H), 8.03 (s, 1H), 7.45 (d, J = 0.9, 1H), 3.92 (t, J = 5.7, 2H), 3.33 (t, J = 5.8, 2H), 2.84 (d, J = 0.9, 3H).

Ex.	A-R ₇	(M+H) ⁺	¹ H NMR
92		354.10	
93		368.20	
94		343.20	
95		343.16	
96		340.13	
97		364.13	
98		368.19	
99		409.18	
100		368.0	(TFA salt): 7.83 (br s, 3H), 7.70-7.67 (m, 2H), 7.61-7.59 (m, 2H), 7.43 (d, J = 0.6, 1H), 7.37 (m, 1H), 7.23 (d, J = 7.6, 1H), 3.75 (app q, J = 5.8, 2H), 3.67 (t, J = 6.9, 2H), 3.16 (m, 2H), 2.79 (t, J = 6.9, 2H), 2.76 (s, 3H).

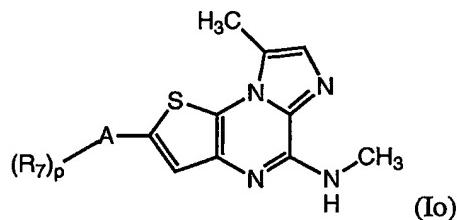
Ex.	A-R ₇	(M+H) ⁺	¹ H NMR
101		327.0	(TFA salt): 7.84 (br s, 3H), 7.67 (br t, J = 5.8, 1H), 7.42 (d, J = 1.0, 1H), 7.29 (s, 1H), 6.96 (app t, J = 2.2, 1H), 6.36 (dd, J = 3.8, 1.7, 1H), 6.10 (dd, J = 3.7, 2.8, 1H), 3.79 (s, 3H), 3.74 (app q, J = 5.9, 2H), 3.15 (m, 2H), 2.71 (d, J = 0.7, 3H).
102		375.9	
103		357.9	
104		357.9	
105		375.9	
106		375.9	

Example 107

N-Bromosuccinimide (5.7055g, 32.0552 mmol) was added in batches, over 5 min, to a cooled (0°C) chloroform (250 mL) solution of Example 5 (6.00 g, 27.4876 mmol). The reaction mixture was stirred for 8 h at 0°C and for an additional 16 h while allowing 5 the bath to thaw to 10°C. The cooling bath was removed and 1 hr later the reaction mixture was washed with water (100 ml, 3X) and brine. It was dried (MgSO_4), filtered and evaporated *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography using a short column (50-60 % EtOAc/hexanes) to afford Example 107 as a fluffy gray solid (6.56 g, 80.3 %). ^1H NMR: 7.54 (br m, 1H), 10 7.48 (s, 1H), 7.34 (s, 1H), 2.96 (d, $J = 4.8$, 3H), 2.63 (s, 3H). (ESI) m/z ($M+\text{H}^+$)⁺ = 297.10/299.10

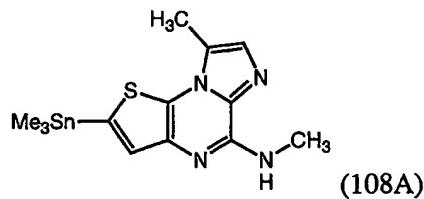
Examples 108-125

15



Compounds having the formula (Io) wherein A-(R_7)_p together have the values listed in Table 8, below, were prepared following Steps A and B below.

20 Step A:



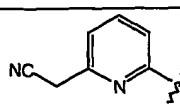
Stannylation of Example 107 (4.064 g, 13.6752 mmol) was set up according to the procedure described for compound 69A. The reaction mixture was quite heterogeneous initially but homogenized after heating. After 40 min of heating, the mixture was cooled to rt and filtered through a pad of celite, and the filtrate was 5 rotovaped. The residue was triturated with ether (~ 100 mL), and the ash-colored solid was filtered and washed with copious ether and dried *in vacuo* (3.2929 g of 108A was retrieved). LC/MS and ^1H NMR analysis of the sample indicated that it contained minor impurities including Example 5; according to LC/MS, the ratio of stannane 108A to Example 5 was greater than 30. ^1H NMR: 7.32 (overlapped signals, 3H), 2.96 (d, $J = 4.9$, 10 3H), 2.69 (d, $J = 0.9$, 3H), 0.40 (s, 9H; 2 satellite peaks are observed with $J = 57.3$, 59.9). (ESI) m/z $(\text{M}+\text{H})^+ = 383.06$.

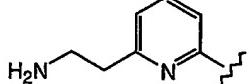
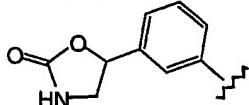
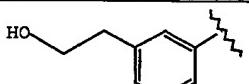
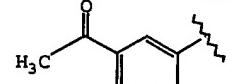
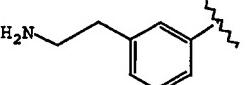
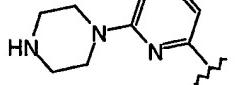
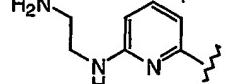
Step B:

Compounds of Examples 108-125 were prepared from stannane 108A following 15 the coupling procedure described above for Examples 89-106, using the desired coupling partner ((R_7)_pA-Br or (R_7)_pA-I) (see, e.g., Preparations 1 - 34 or commercially available compounds). The resultant product was purified with flash chromatography, recrystallization and/or PREP-HPLC and was obtained as a free base or TFA salt. For Examples 109, 118, and 115, the left amino side chain (e.g., attached to the pyridyl or 20 phenyl rings) was deprotected under standard conditions (TFA/CH₂Cl₂). For Example 122, the compound was deacylated following the procedure described above for Examples 102-106.

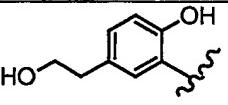
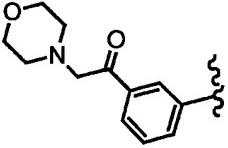
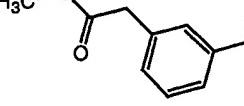
TABLE 8

25

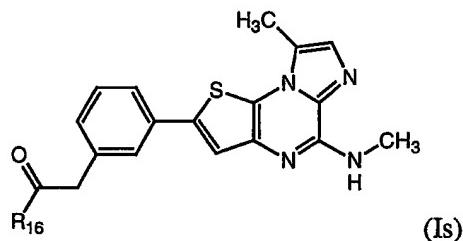
Ex. #	A-(R_7) _p	$(\text{M}+\text{H})^+$	Other Data (^1H NMR)
108		335.16	

Ex. #	A-(R ₇) _p	(M+H) ⁺	Other Data (¹ H NMR)
109		339.21	
110		380.15	(TFA salt): 7.80 (s, 1H), 7.79 (m, 1H), 7.76 (m, 2H), 7.53 (app t, J = 7.8, 1H), 7.45 (s, 1H), 7.40 (d, J = 7.7, 1H), 5.68 (app t, J = 8.1, 1H), 3.93 (app t, J = 8.7, 1H), 3.43 (app t, J = 8.3, 1H), 3.03 (s, 3H), 2.75 (d, J = 0.6, 3H).
111		339.0	(Free base): 7.73 (s, 1H), 7.60-7.59 (m, 2H), 7.46 (br q, J = 4.8, 1H), 7.37-7.34 (m, 2H), 7.21 (app d, J = 7.6, 1H), 4.68 (t, J = 5.2, 1H), 3.67 (m, 2H), 2.99 (d, J = 4.6, 3H), 2.79 (t, J = 7.0, 2H), 2.73 (d, J = 0.6, 3H).
112		337.0	
113		338.0	
114		380.22	
115		354.24	

Ex. #	A-(R ₇) _p	(M+H) ⁺	Other Data (¹ H NMR)
116		355.20	(TFA salt): 7.84 (s, 1H), 7.46 (dd, J = 8.1, 7.5, 1H), 7.45 (s, 1H), 7.16 (d, J = 7.0, 1H), 6.47 (d, J = 8.3, 1H), 3.61 (t, J = 6.1, 2H), 3.39 (t, J = 6.1, 2H), 3.03 (s, 3H), 2.75 (d, J = 0.6, 3H).
117		353.16	
118		324.0	(TFA salt): 8.23 (br s, 3H), 7.86 (s, 1H), 7.83 (d, J = 7.9, 1H), 7.80 (s, 1H), 7.67 (br s, 1H), 7.52 (app t, J = 7.8, 1H), 7.43 (d, J = 7.9, 1H), 7.41 (d, J = 0.9, 1H), 4.12 (q, J = 5.8, 2H), 3.00 (d, J = 3.4, 3H), 2.74 (d, J = 0.6, 3H).
119		380.23	(Free base): 7.95 (br t, J = 5.4, 1H), 7.76 (s, 1H), 7.62 (br d, J = 7.9, 1H), 7.58 (m, 1H), 7.45 (br q, J = 4.4, 1H), 7.37 (app t, J = 7.6, 1H), 7.36 (d, J = 0.9, 1H), 7.19 (d, J = 7.7, 1H), 2.99 (d, J = 4.8, 3H), 2.77 (t, J = 7.4, 2H), 2.73 (d, J = 0.6, 3H), 1.80 (s, 3H).
120		416.17	(Free base): 7.78 (s, 1H), 7.65 (m, 1H), 7.63 (d m, J = 7.7, 1H), 7.47

Ex. #	A-(R ₇) _p	(M+H) ⁺	Other Data (¹ H NMR)
			(q, J = 4.7, 1H), 7.39 (app t, J = 7.6, 1H), 7.36 (d, J = 0.9, 1H), 7.24 (d, J = 7.6, 1H), 7.13 (t, J = 5.8, 1H), 3.25 (m, 2H), 2.99 (d, J = 4.9, 3H), 2.85 (s, 3H), 2.84 (t, J = 7.5, 2H), 2.74 (d, J = 0.6, 3H).
121		285.09	(TFA salt): 7.78 (d, J = 1.2, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 6.96 (d, J = 3.4, 1H), 6.66 (dd, J = 3.4, 1.9, 1H), 3.02 (s, 3H), 2.71 (d, J = 0.9, 3H).
122		355.0	
123		422.24	
124		380.22	
125		367.16	(Free base): 7.75 (s, 1H), 7.69 (m, 1H), 7.65 (m, 1H), 7.48 (m, 1H, NH), 7.41 (app t, J = 7.8, 1H), 7.36 (d, J = 0.9, 1H), 7.25 (m, 1H), 3.77 (s, 2H), 3.65 (s, 3H), 2.99 (d, J = 4.5, 3H), 2.73 (d, J = 0.7, 3H).

Ex. #	A-(R ₇) _p	(M+H) ⁺	Other Data (¹ H NMR)
126		353.15	

Examples 127-129

Examples 127-129 having formula (I)s above, wherein R₁₆ is OH (Ex. 127), NH₂ (Ex. 128), and morpholinyl (Ex. 129), were each prepared from Example 125 as follows:

10

Example 127:

NaOH (200 uL of 1.0 M/H₂O) was added to a MeOH (2.0 mL) suspension of Example 125 (33 mg, 0.090 mmol) and the mixture was stirred at 70°C for 2.5 h. The reaction mixture was diluted with MeOH and submitted to a PREP-HPLC to afford the 15 TFA salt of Example 127 as a yellow solid (25 mg). (ESI) m/z (M+H)⁺ = 353.15.

Example 128:

MeOH (5.0 mL) was added into a Parr bomb containing Example 125 (40.7 mg, 0.1111 mmol), and dry ammonia gas was bubbled through it for 5 min. The apparatus 20 was capped and heated at 70°C for 16.25 h. It was cooled to rt and the suspension filtered and washed MeOH. The solid was dissolved in DMF and submitted to a PREP-HPLC to afford the TFA salt of Example 128 as an off-white solid (17.5 mg). ¹H NMR: 7.72 (s, 1H), 7.67 (d, J = 7.6, 1H), 7.63 (app br s, 1H), 7.53 (br s, 1H), 7.44 (br s, 1H),

7.40 (app t, J = 7.6, 1H), 7.26 (d, J = 7.6, 1H), 6.94 (br s, 1H), 3.45 (s, 2H), 3.03 (s, 3H), 2.75 (d, J = 0.6, 3H). (ESI) m/z (M+H)⁺ = 352.15.

Example 129:

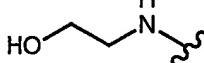
5 A mixture of morpholine (2.0 mL) and Example 125 (43.1 mg, 0.1176 mmol) was heated at 120 °C for 46.5 h. The volatile component was removed *in vacuo* and the resulting crude material was passed through an SAX column (prewashed with MeOH; column eluted with MeOH) to remove an impurity (*e.g.*, Example 127). The solvent was removed *in vacuo*, and a silica gel mesh was prepared from the residue and submitted to
10 flash chromatography (0-5 % MeOH/EtOAc) to afford Example 129 as a light yellow semi-solid (17.5 mg). (ESI) m/z (M+H)⁺ = 422.19.

Examples 130-132

15 Examples 130-132 having formula (Is) above, were prepared from Example 125 and the respective amines according to the procedure described for Example 129, with a slight modification where in the reaction was heated at 110 °C until the ester was totally consumed. For Examples 130 and 132, the volatile component was removed *in vacuo* and the crude residue was purified on a Prep-HPLC. For Example 131, after the reaction
20 mixture was allowed to cool to room temperature, the suspension was filtered and washed with copious EtOAc and MeOH.

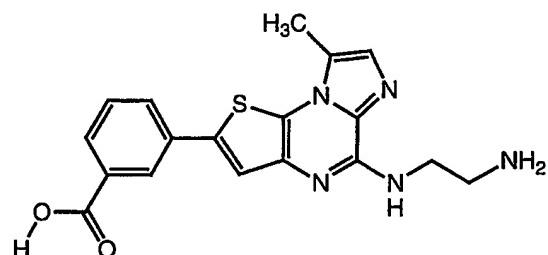
TABLE 9

Ex. #	R ₁₆ in (Is)	(M+H) ⁺	Other Data (¹ H NMR)
130		423.34	
131		367.19	

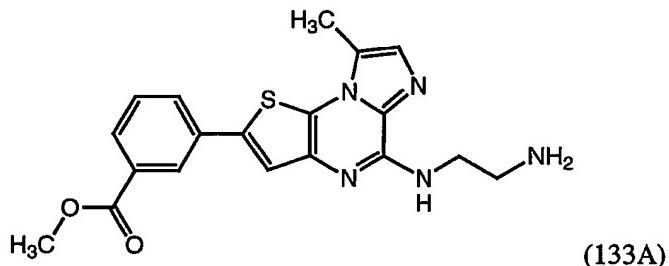
Ex. #	R ₁₆ in (Is)	(M+H) ⁺	Other Data (¹ H NMR)
132		396.32	

Example 133

5



Step A:

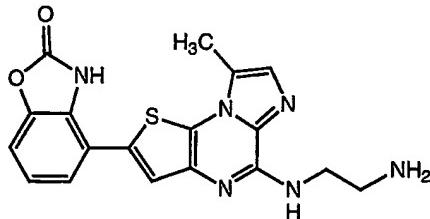


10

The TFA salt of compound 133A was obtained following the same procedure described above for Examples 69-87.

Step B:

Compound 133A was treated with MeOH (2.0 mL) and NaOH (0.20 mL of 1.0 M/H₂O, 0.20 mmol), and heated with an oil bath (~ 65°C) for 95 min. It was cooled to rt, diluted with MeOH and purified on a PREP-HPLC. The TFA salt of Example 130 was obtained as an off-white solid (~13 mg). (ESI) m/z (M+H)⁺ = 368.21.

Example 134

5 A dioxane (3.0 mL) solution of stannane 69A (100 mg, 0.196 mmol) and compound P13 (~ 3 mol equiv.) was degassed with nitrogen and treated with $\text{Pd}(\text{Ph}_3\text{P})_4$ (7.0 mg, 0.0061 mmol) and LiCl (30 mg, 0.708 mmol). The reaction mixture was stirred at 100°C for 16 h, cooled to rt, diluted with EtOAc, and evaporated onto silica gel. The resulting silica gel mesh was submitted to flash chromatography to afford the Boc-
10 protected precursor to Example 134. The compound was deprotected as described for Examples 60-68. ^1H NMR: 11.95 (s, 1H), 7.83 (br s, 3H), 7.72 (br t, J = 5.7, 1H), 7.68 (s, 1H), 7.45 (d, J = 0.9, 1H), 7.38 (dd, J = 7.9, 0.6, 1H), 7.34 (dd, J = 7.9, 0.6, 1H), 7.20 (app t, J = 8.1, 1H), 3.75 (app q, J = 5.8, 2H), 3.17 (app br s, 2H), 2.76 (s, 3H). (ESI) m/z (M+H) $^+$ = 381.0.

15

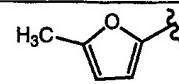
Examples 135-136

To prepare compounds having the formula (Im) above wherein A-R₇ are as in TABLE 10, toluene/acetone/water (1:1:0.5, 4.5 mL) and K₂CO₃ were added to a mixture
20 of bromide 59A (100 mg, 0.2346 mmol) and (A-R₇)B(OH)₂ (~2.0 mol. equiv). After nitrogen was bubbled through the biphasic mixture for a few minutes, the mixture was treated with $\text{PdCl}_2(\text{dppf})\text{-CH}_2\text{Cl}_2$ complex (2 mg, 0.002 mmol) and heated at 70°C until complete consumption of the bromide. The reaction mixture was cooled to rt, diluted with EtOAc and washed with water and brine. It was dried (MgSO_4), filtered, and
25 evaporated *in vacuo*. A silica gel mesh was prepared from the crude material and submitted to a standard flash chromatography protocol to afford Boc-protected amines.

The compounds were deprotected as described for Examples 60-68 to afford Examples 135 and 136 as the TFA salt.

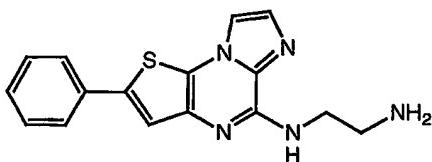
TABLE 10

5

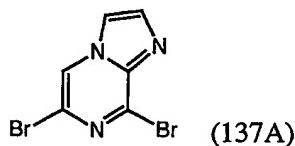
Ex. #	A-R ₇	(M+H) ⁺
135		313.0
136		328.0

Example 137

10



Step A:



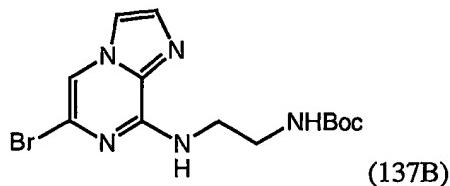
15

Ethanol (10.0 mL) and chloroacetaldehyde (2.6953 g of 50 % by weight solution in water, 17.17 mmol) were added into a pressure tube containing 2-amino-3,5-dibromopyrazine (2.015 gm, 7.97 mmol). The heterogeneous reaction mixture was stirred at 70°C. The reaction mixture assumed a homogenous appearance after heating began, and precipitation started to appear 3 h later. After a total of 22 h of heating, the reaction mixture was cooled to rt. The precipitate was filtered, washed with EtOH (~10

20

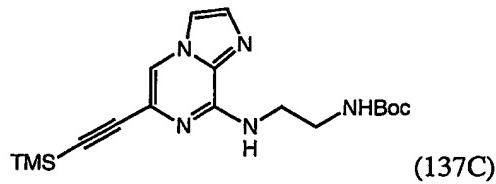
mL), and exposed to high vacuum to afford impure imidazopyrazine 137A as an ash-colored solid (1.699 g). ^1H NMR: 9.03 (s, 1H), 8.24 (d, J = 0.9, 1H), 7.91 (d, J = 1.2, 1H). (ESI) m/z (M+H) $^+$ = 277.79.

5 Step B:



The impure imidazopyrazine 137A was added to a THF (10.0 mL) solution of *tert*-butyl *N*-(2-aminoethyl)carbamate (1.1232 g, 7.0104 mmol). In less than a minute, 10 the homogenous reaction mixture formed a solid. TEA (2.0 mL, 14.349 mmol) was added and the mixture was stirred at rt for 3.75 h and at 64 °C for 4.5 h. The side of the flask was washed with THF (8.0 mL), and it was heated for an additional 2 h. It was cooled to rt and the precipitate filtered and washed with EtOAc. A silica gel mesh was prepared from the filtrate and submitted to flash chromatography (40-50 % 15 EtOAc/hexanes) to afford bromide 137B as a faint yellow solid (1.495 g, a two step combined yield of 52.7 %). ^1H NMR (CDCl_3 , δ = 7.26 ppm; 300 MHz): 7.58 (s, 1H), 7.50 (d, J = 1.1, 1H), 7.45 (d, J = 1.5, 1H), 6.69 (br s, 1H), 5.14 (br s, 1H), 3.73 (m, 2H), 3.45 (m, 2H). 1.43 (s, 9H). (ESI) m/z (M+H) $^+$ = 355.93/357.93.

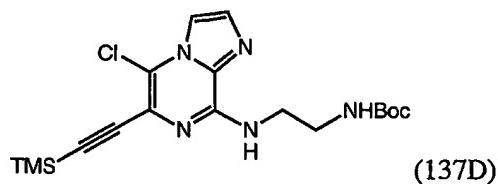
20 Step C:



The coupling of bromide 137B with (trimethylsilyl)acetylene was conducted according to Example 1, Step F to afford alkyne 137C as an off-white solid in 80.4 %

yield. ^1H NMR: 8.11 (s, 1H), 7.81 (d, J = 1.3, 1H), 7.60 (br t, J = 5.2, 1H), 7.53 (d, J = 1.2, 1H), 6.94 (br t, J = 5.2, 1H), 3.48 (m, 2H), 3.19 (m, 2H), 1.37 (s, 9H), 0.24 (s, 9H). (ESI) m/z ($M+H$)⁺ = 374.16.

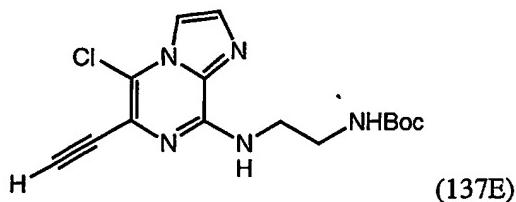
5 Step D:



The chlorination of compound 137C was conducted according to Example 1, Step 10 G to afford chloride 137D as an off-white dense solid in 87.8 % yield. ^1H NMR (CDCl_3 , δ = 7.26 ppm; 500 MHz): 7.67 (s, 1H), 7.56 (s, 1H), 6.27 (app br s, 1H), 4.99 (app br s, 1H), 3.75 (m, 2H), 3.45 (m, 2H), 1.43 (s, 9H), 0.30 (s, 9H). (ESI) m/z ($M+H$)⁺ = 408.09.

Step E:

15



Example 137D was desilylated as described in Example 9 to form chloroalkyne 137E as an off-white solid. ^1H NMR: 8.00 (d, J = 1.2, 1H), 7.82 (br t, J = 5.7, 1H), 7.67 (d, J = 1.2, 1H), 6.93 (br t, J = 5.5, 1H), 4.51 (s, 1H), 3.47 (app q, J = 6.1, 2H), 3.19 (app q, J = 6.1, 2H), 1.36 (s, 9H).

Step F: Example 137

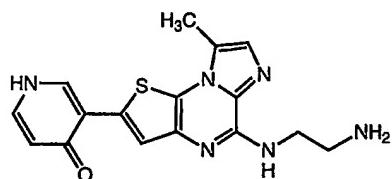
Chloroalkyne 137E was coupled with an iodobenzene and cyclized as described above for Examples 17-27. Deprotection followed by HCl salt formation likewise

proceeded as described in Example 9, Step D, to afford Example 137 as an HCl salt. ^1H -NMR of salt: 8.28 (d, $J = 0.9$, 1H), 7.78-7.70 (m, 8H), 7.48 (m, 2H), 7.38 (m, 1H), 3.75 (app q, $J = 5.9$, 2H), 3.14 (app t, $J = 6.1$, 2H). (ESI) m/z (M+H) $^+$ = 310.31.

5

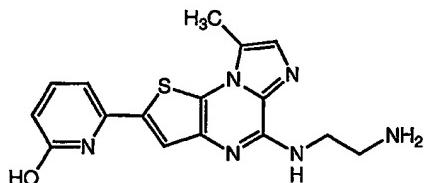
Example 138

BBr₃ (1.5 mL, 1.0 M/CH₂Cl₂) was added to a cooled (0°C) CH₂Cl₂ (2.0 mL) solution of the the Boc-protected precursor of Example 51 (methyl ether) (70 mg, 0.154 mmol) and stirred for 50 min. The bath was removed, and the heterogeneous reaction mixture was stirred for an additional 14 h and quenched with MeOH. The volatile component was removed *in vacuo*, and the residue was dissolved in a MeOH/H₂O mixture and purified on a PREP-HPLC to afford the TFA salt of Example 138 as light yellow solid (13.7 mg). (ESI) m/z (M+H) $^+$ = 341.12.

Example 139

20

Example 139 was prepared following a similar procedure to that described above for Examples 28-55, starting from P18. In this case, O-demethylation occurred during the cyclization step. (ESI) m/z (M+H) $^+$ = 341.12.

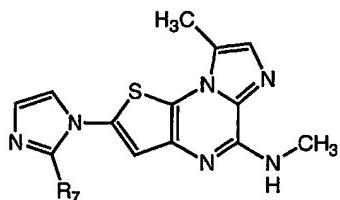
Example 140

5

A mixture of MeOH (3.0 mL) and 48 % HBr (1.0 mL) was added to the Boc-protected precursor to Example 69 (115 mg, 0.2530 mmol). The resulting heterogeneous mixture was stirred at rt for 40 min. Water (1.0 mL) was added and 20 min later it was lowered into a 70°C oil bath and heated for 2.5 hr. LC/MS analysis indicated that the 10 methyl ether was unaffected and only the Boc group was removed. The heterogeneous reaction mixture was cooled to rt and the suspension (an HBr salt of Example 69) was filtered and washed with MeOH and dried *in vacuo* (off-white solid, 116.8 mg).

Trimethylsilyl chloride (150 uL, 1.1819 mmol) was added to a CH₃CN (4.0 mL) suspension of the HBr salt of Example 69 and NaI (165.7 mg, 1.1435 mmol). The 15 heterogeneous mixture was stirred at rt for 22 h. Additional NaI (142.1 mg, 0.9807 mmol) and trimethylsilyl chloride (150 uL, 1.1819 mmol) were added and the mixture was stirred at rt for 26 h and at 70 °C for 24 h. The reaction was quenched with MeOH (4.0 mL) and heated at 70 °C for 10 min. It was cooled to rt and the volatile component was removed *in vacuo*. The crude material was dissolved in DMF and purified on a 20 PREP-HPLC to afford the TFA salt of Example 140 as a yellow solid (39 mg). (ESI) m/z (M+H)⁺ = 341.12.

Examples 141-142



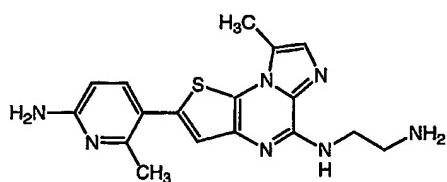
To prepare Example 141 wherein *R*₇ = hydrogen, CuI (51.2 mg, 0.2689 mmol), imidazole (1.067 g, 15.69 mmol) and Example 107 (51.9 mg, 0.1746 mmol) were mixed 5 in a vial and heated at 120°C for 63 h. LC/MS analysis of the crude mixture indicated that it contained Example 141 and the debrominated product, *i.e.* Example 5, in a 3:2 ratio. The reaction mixture was cooled to rt, dissolved in MeOH and purified on a PREP-HPLC. The TFA salt of Example 141 was obtained as a yellow dense foam containing a minor amount of an unidentified impurity (26.9 mg). ¹H NMR: 9.17 (s, 1H), 8.07 (s, 1H), 7.76 (overlapping signals, 2H), 7.66 (s, 1H), 7.42 (d, *J* = 0.9, 1H), 2.99 (d, *J* = 2.4, 3H), 2.70 (d, *J* = 0.9, 3H). (ESI) m/z (M+H)⁺ = 285.16.

10

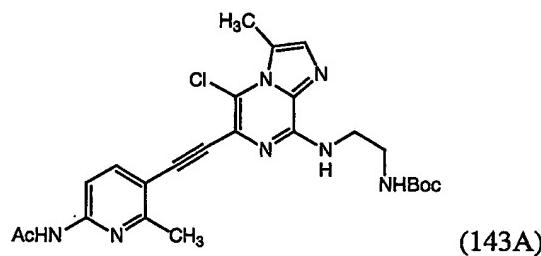
Example 142 wherein *R*₇ = methyl was prepared as a free base following the same procedure as for Example 141, starting with 2-methyl imidazole instead of imidazole. (ESI) m/z (M+H)⁺ = 299.12.

15

Example 143



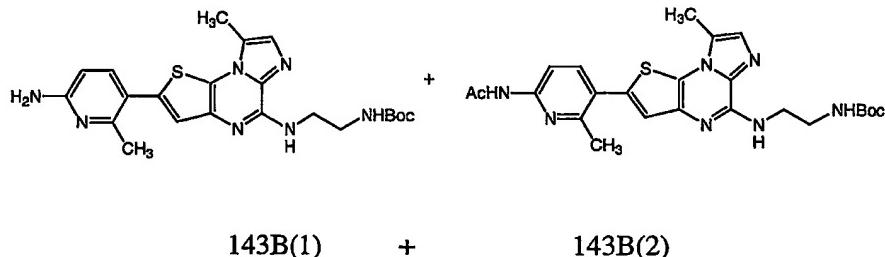
20 Step A:



Aminopyridine P15 was coupled with Example 9A according to the procedure described for Examples 28-55 to produce 143A.

5

Step B:



10

Compound 143A was cyclized according to the procedure described for Examples 28-58 to produce a mixture of 143B(1) and 143B(2) with a ~1:5 HPLC ratio (20 mg).

Step C:

15

Hydrazine (2.0 mL) was added to the mixture from Step B and the reaction mixture was stirred at 100°C for 2 h. After it was allowed to cool to rt, the hydrazine was removed *in vacuo* to afford crude compound 143B1. The Boc group of 143B1 was removed following Example 1, Step I, to afford Example 143 as the TFA salt. (ESI) m/z (M+H)⁺ = 354.26.

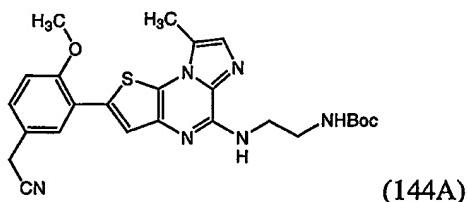
20

Examples 144-146



Step A:

5



Compound 144A was prepared by coupling 3-bromo-4-methoxy-phenylacetonitrile with compound 69A according to the process described for Examples 10 89-106.

Step B: Examples 144-146

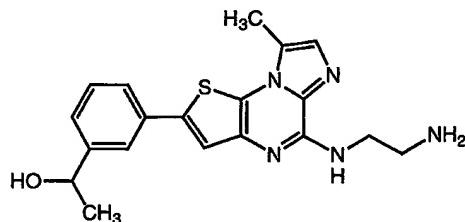
BBBr₃ (380 uL of 1.0 M/CH₂Cl₂) was added to a cooled (-30 °C) CH₂Cl₂ (2.0 mL) solution of compound 144A (61.7 mg). The reaction mixture was stirred for 5 h by 15 allowing the bath to thaw to 0 °C. It was quenched with MeOH, solvent was removed *in vacuo*, and the residue was purified on a PREP-HPLC. Three compounds having the above formula (Ip), wherein R₁₆ has the values listed in Table 11, were isolated as TFA salts: Example 144 (18.7 mg), Example 145 (6.2 mg), and Example 146 (4.2 mg).

20

TABLE 11

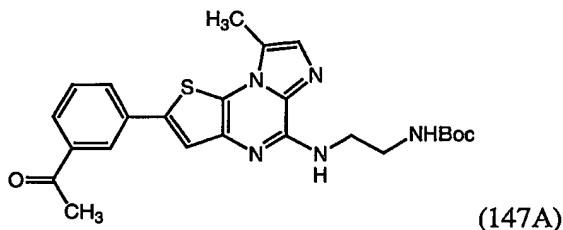
Ex. #	R ₁₆	(M+H) ⁺
144	-CN	393.0

145	-C(=O)NH ₂	411.0
146	-CO ₂ Me	426.0

Example 147

5

Step A:

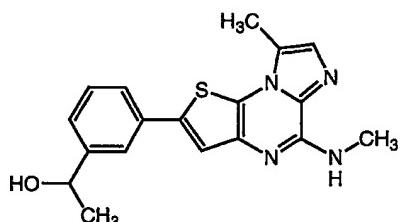


Compound 147A was prepared following the procedure of Examples 89-106 using 3-iodoacetophenone as the halide-coupling component.

10

Step B:

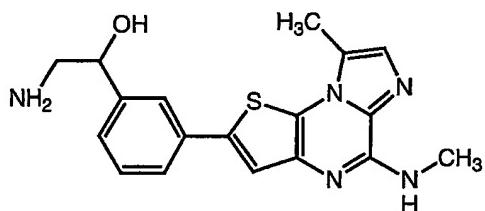
Compound 147A (51.1 mg, 0.11 mmol) was dissolved in EtOH (8.0 mL) and treated with NaBH₄ (7.0 mg, 0.185 mmol), and the reaction mixture was stirred at rt for 2 h. After the solvent was removed *in vacuo*, the residue was dissolved in EtOAc and washed with sat'd NH₄Cl and brine. The organic layer was dried (MgSO₄), filtered and evaporated *in vacuo* to afford Boc-protected precursor of Example 147 as a yellow solid (46 mg). The compound was deprotected following the procedure in Example 59 to afford the TFA salt of Example 147. ¹H-NMR: 7.86 (br s, 3H), 7.69-7.64 (m, 3H), 7.43-7.39 (m, 3H), 7.33 (br d, J = 7.3, 1H), 4.79 (q, J = 6.3, 1H), 3.75 (app q, J = 5.5, 2H), 3.16 (m, 2H), 2.76 (s, 3H), 1.38 (d, J = 6.5, 3H). (ESI) m/z (M+H)⁺ = 368.1.

Example 148

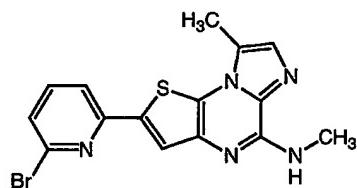
5

The same coupling and reduction procedures as described for Example 147 were applied to Example 108A to produce Example 148 as the free base. (ESI) m/z (M+H)⁺ = 339.0.

10

Example 149

THF/H₂O (3.0 mL of 3:1 mixture) and LiOH (31.5 mg) were added to Example 15 110 (44 mg, 0.1451 mmol). The reaction mixture was heated at 70°C for 7.5 h, additional LiOH (54 mg) was added, then 14.25 h later water (0.5 mL) was added, and 8.45 h after that THF (2.0 mL) was added. The reaction mixture was heated for an additional 53 h and allowed to cool to rt. It was diluted with MeOH, slightly acidified with TFA, and loaded onto a MeOH pre-washed SCX column. The column was washed 20 with MeOH and the compound eluted with 2.0 M NH₃/MeOH. The volatile component was removed *in vacuo* and the residue dissolved in MeOH and purified on a PREP-HPLC to afford the TFA salt of Example 149 as an off-white foam. Recrystallizing from MeOH afforded an off-white solid (~ 5.5 mg). (ESI) m/z (M+H)⁺ = 354.13.

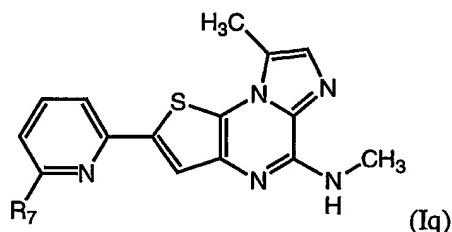
Example 150

5

2,6-dibromopyridine was coupled with stannane 108A according to the procedure described for Examples 69-87 to afford Example 150 along with minor impurities.

Examples 151-154

10

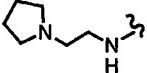
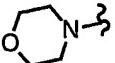
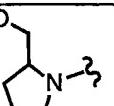


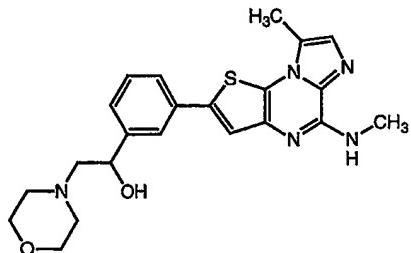
A mixture of Example 150 (25.3 mg, ~0.0676 mmol) and an appropriate R₇H amine (*i.e.*, *N,N*-dimethylethylenediamine [504.6 mg, 5.718 mmol] for Example 151) was heated at 110°C for 6.5 h and at 120°C for 37 h. It was allowed to cool to rt, diluted with MeOH and purified on a PREP-HPLC to afford the TFA salt of pyridine of formula (Iq), above, wherein R₇ is as in Table 12, depending on the amine selected. The salt was free-based according to the procedure described for Example 5 to afford the desired pyridine as a yellow foam (*e.g.*, 10.5 mg for Example 151).

15
20

TABLE 12

Ex. #	R ₇	(M+H) ⁺
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151	-NH(CH ₂) ₂ N(Me) ₂	382.16
152		408.20
153		381.19
154		395.22

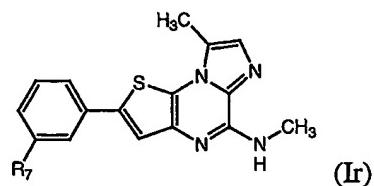
Example 155

5

NaBH₄ (14.2 mg, 0.375 mmol) was added to a cooled (0°C) MeOH (3.0 mL) suspension of Example 123 (42 mg, 0.100 mmol). The reaction mixture was stirred for 2.15 h at 0°C and for 2 h at rt. NaBH₄ (14.3 mg, 0.3780 mmol) was added and stirring continued for 22.5 h. The reaction was quenched with acetone (1.0 mL) and the solvent removed *in vacuo*. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (0-10 % MeOH/EtOAc) to afford Example 155. The alcohol was further purified on a PREP-HPLC to afford the TFA salt of Example 155 as an off-white solid (35 mg). (ESI) m/z (M+H)⁺ = 424.31.

15

Examples 156-157

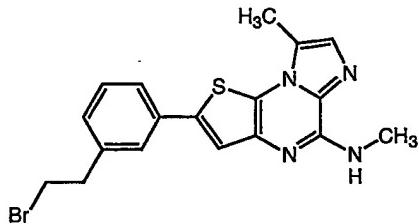


Compounds having the formula (Ir), wherein R₇ has the values listed in Table 13, were prepared following the same procedure as for Example 155, starting with the
5 appropriate ketone prepared as described above for Examples 108-125 (e.g., Ex. 124 was used to make Example 157).

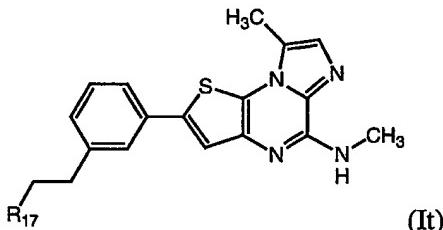
TABLE 13

10

Ex. #	R ₇	(M+H) ⁺	¹ H NMR
156		405.24	(TFA salt): 14.29 (br s, 1H), 9.06 (s, 1H), 7.78 (s, 1H), 7.76 (m, 1H), 7.74 (app t, J = 1.7, 1H), 7.72 (m, 1H), 7.68 (app t, J = 1.5, 1H), 7.48 (app t, J = 7.7, 1H), 7.41 (d, J = 0.9, 1H), 7.38 (d, J = 7.7, 1H), 6.11 (br s, 1H), 5.05 (dd, J = 8.4, 3.2, 1H), 4.51 (dd, J = 13.8, 3.4, 1H), 4.35 (dd, J = 13.9, 8.4, 1H), 3.00 (d, J = 3.7, 3H), 2.75 (d, J = 0.9, 3H).
157		382.22	

Example 158

5 Stannane 108A (80.8 mg, 0.2120 mmol), dibromide P26 (132.8 mg, ~0.4869 mmol), $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ (13.0, 0.0185 mmol), KF (27.5 mg, 0.4733 mmol) and DMF (2.6 mL) were sequentially added into a vial. Nitrogen was bubbled through the heterogeneous mixture for about a minute; it was heated at 90°C for 4.5 h and allowed to cool to rt. The solvent was removed *in vacuo* and a silica gel mesh was prepared and
10 submitted to flash chromatography (50-60 % EtOAc/hexanes) to afford impure Example 158 (33 mg).

Examples 159-173

15 To prepare compounds having the formula (It), wherein R_{17} has the values listed in Table 14, DMF (2.0 mL), an appropriate heterocycle or amine (*i.e.*, morpholine for Example 159 [150 uL, 1.720 mmol]), and K_2CO_3 (13.1 mg, 0.0948 mmol) were added
20 into a vial containing impure Example 158 (33 mg, <). The reaction mixture was stirred at 90°C for 2.75 h, cooled to rt and the solvent removed *in vacuo*. The residue was

dissolved in MeOH and submitted to a PREP-HPLC to afford the TFA salt of the desired compound. The TFA salt was converted to the free-base by the following route:

- The material obtained from the PREP-HPLC was dissolved in MeOH and loaded onto an MeOH-prewashed SCX column. The column was washed with methanol and then the compound eluted from the column with 2.0 M NH₃/MeOH. The solvent was removed *in vacuo* to afford the free-base form of the desired compound.
- 5

For Examples 172 and 173, the respective starting materials which were available as HCl salts were free-based, by employing the above SCX methodology, before they were submitted to the alkylation step.

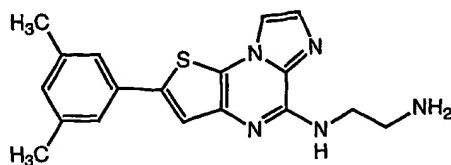
10

TABLE 14

Ex. #	R ₁₇	(M+H) ⁺	¹ H NMR
159		408.18	
160		389.20	
161		421.27	
162		392.24	
163		407.25	
164		435.31	

Ex. #	R ₁₇	(M+H) ⁺	¹ H NMR
165		449.27	
166		421.21	(Free base): 7.76 (s, 1H), 7.73 (br s, 1H), 7.65 (m, 1H), 7.59 (m, 1H), 7.47 (q, J = 4.7, 1H), 7.37-7.34 (m, 2H), 7.23 (d, J = 7.7, 1H), 3.16 (m, 2H), 3.02 (s, 2H), 2.99 (d, J = 4.9, 3H), 2.82 (m, 2H), 2.73 (d, J = 0.6, 3H), 2.67-2.64 (m, 4H).
167	-N(CH ₃) ₂	366.27	
168	-NH(CH ₂) ₂ OH	382.23	
169		417.16	
170		405.13	
171		434.09	
172		395.18	
173		409.18	

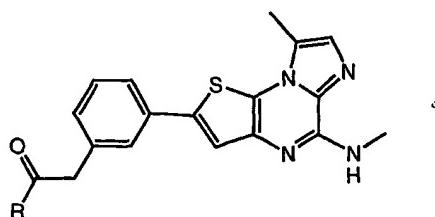
Example 174



The HCl salt of Example 174 was prepared as described for Example 137, using 5-iodo-*m*-xylene instead of iodobenzene. $^1\text{H-NMR}$: 8.24 (d, $J = 0.9$, 1H), 7.82 (br s, 3H), 5 7.77 (br t, $J = 5.7$, 1H), 7.70 (d, $J = 1.2$, 1H), 7.65 (s, 1H), 7.36 (s, 2H), 7.02 (s, 1H), 3.76 (app q, $J = 5.9$, 2H), 3.15 (app t, $J = 6.1$, 2H), 2.34 (s, 6H). (ESI) m/z ($M+\text{H}$) $^+ = 338.21$.

Examples 175-176

10 Me₃Al (350 μl of 2.0 M/hexanes) was added into a THF (2.0 mL) semi-solution of the respective piperazine (0.7151 mmol) and the resultant solution was stirred for 15 min. Example 125 (42.3 mg, 0.1154 mmol) was added in one batch and the heterogeneous mixture was heated at 70 °C for 14.25 h. It was allowed to cool to room temperature and quenched with MeOH. After the volatile component was removed *in vacuo*, the residue 15 was treated with wet DMF, the precipitate filtered, and the filtrate was submitted to a Prep-HPLC. The resulting material was free-based according to the procedure described for Examples 155-164.

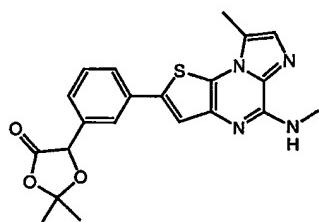


20

TABLE 15

Ex. #	R	(M+H) $^+$	Other Data ($^1\text{H NMR}$)
175		421.14	

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
176		435.23	

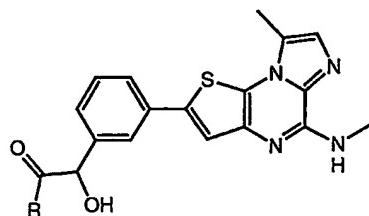
Example 177

5

LiCl (30.8, 0.7266 mmol) and Pd(PPh₃)₄ (9.1 mg, 0.0079 mmol) were sequentially added into a mixture of Stannane 108A, (80.6mg, 0.2115 mmol) and triflate P35 (149.6 mg, 0.4397 mmol) in dioxane (3.0 mL). The reaction mixture was flushed with N₂ and heated at 90 °C for 4.5 h. After it was allowed to cool to room temperature, the volatile component was removed *in vacuo*. A silica gel mesh was prepared and submitted to flash chromatography (60-75% EtOAc/hexanes) to afford Example 177 (86.5 mg) as an off-white solid, containing Example 5 and Ph₃PO impurities. The sample was recrystallized from EtOAc to afford pure Example 177 as a dull-yellow solid (32.1mg). ¹H NMR: 7.83 (m, 1H), 7.82 (s, 1H), 7.75 (m, 1H), 7.53 (app t, J = 7.8, 1H), 7.51 (br s, 1H), 7.40 (app d, J = 7.7, 1H), 7.37 (d, J = 1.0, 1H), 5.84 (s, 1H), 2.99 (d, J = 4.7, 3H), 2.74 (d, J = 0.6, 3H), 1.76 (s, 3H), 1.69 (s, 3H). (ESI) m/z (M+H)⁺ = 409.12.

Examples 178-182

20



Examples 178-182 having formula above, wherein R is OH (Ex. 178), NH₂ (Ex. 179), N-methylpypirizinyl (Ex. 180), morpholinyl (Ex. 181), OMe (Ex. 182) were each
5 prepared from Example 177 as follows:

Example 178:

The mother liquor retrieved from the recrystallization of Example 177 was rotovaped, and the resulting crude material was treated with MeOH (4.0 mL) and NaOH 10 (260 uL of 1.0 M/H₂O; 0.260 mmol) and heated at 70 °C for 5 h. After it was allowed to cool to room temperature, the volatile component was removed *in vacuo* and the crude material was purified with Prep-HPLC, followed by recrystallization (MeOH) to afford the free-base form of Example 178 as an off-white solid (6 mg). (ESI) m/z (M+H)⁺ = 369.19.
15

Example 179:

Anhydrous NH₃ was bubbled through a mixture of MeOH (8.0 mL) and Example 177 (51.6 mg, 0.1264 mmol) in a Parr bomb for 7 min. The apparatus was capped and heated at 70 °C for 27 h. It was allowed to cool to room temperature, and the suspension 20 was filtered and washed with MeOH to afford Example 179 as an off-white solid (27.6 mg). (ESI) m/z (M+H)⁺ = 368.22.

Example 180:

A mixture of N-methyl piperazine (1.0 mL) and Example 177 (40.2 mg, 0.0985 25 mmol) was heated at 70 °C for 4.25 h. The volatile component was removed *in vacuo*, and the crude material was submitted to a Prep-HPLC to afford the TFA salt of Example

180. The salt was free-based according to the procedure described for Examples 159-173 to afford Example 180 as an off-white foam (24.7 mg). (ESI) m/z (M+H)⁺ = 451.23.

Example 181:

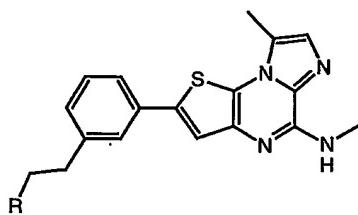
5 A mixture of morpholine (1.0 mL) and Example 177 (43.7 mg, 0.1071 mmol) was heated at 70 °C for 2 h. The volatile component was removed *in vacuo* and the resulting crude material was submitted to a Prep-HPLC to afford Example 181 as a light yellow solid (15.8 mg). Interestingly the material obtained from the Prep-HPLC purification was in a free-base form as confirmed by F-19 NMR. (ESI) m/z (M+H)⁺ = 438.10.

10

Example 182:

MeOH (5.0 mL) was added into a mixture of K₂CO₃ (9.3 mg, 0.0673 mmol) and Example 177 (47 mg, 0.1152 mmol), and the heterogeneous reaction mixture was vigorously stirred for 2 h. A silica gel mesh was prepared directly from the reaction 15 mixture and submitted to flash chromatography (0-5% MeOH/EtOAc) to afford Example 182 as an off-white solid (13.0 mg). (ESI) m/z (M+H)⁺ = 383.17.

Examples 183-190



Examples 183-190 having formula above, wherein R is shown in Table 16, were prepared from the free-base form of Example 113 as follows:

25 **Example 183:**

E_t₃N (40 uL, 0.287 mmol) and Me₂NSO₂Cl (30 uL, 0.2793 mmol) were added into a THF (2.0 mL) suspension of Example 113 (43.7 mg, 0.1296 mmol). The reaction mixture was stirred for 18 h, additional Me₂NSO₂Cl (50 uL, 0.466 mmol) was added and it was stirred for 24 h. MeOH (2.5 mL) was added and the mixture was heated to a reflux briefly and cooled to room temperature. The volatile component was removed *in vacuo*, and the residue was submitted to a Prep-HPLC purification to afford the TFA salt of Example 183 as a white solid (42.7 mg).

Example 184:

MeOH (2.0 mL) was added into a mixture of Example 113 (30.5 mg, 0.090 mmol) and potassium cyanate (118.7 mg, 1.4633 mmol). Two pipet drops of acetic acid were added and the reaction mixture was vigorously stirred for 1.75 h. It was then diluted with DMF, filtered and submitted to a Prep-HPLC to afford the TFA salt of Example 184 as an off-white solid (20.5 mg).

15

Example 185:

K₂CO₃ (10.1 mg, 0.073 mmol), DMF (2.0 mL) and bromoacetamide (15.4, 0.1116 mmol) were sequentially added into a flask containing Example 113 (31.0 mg, 0.0919 mmol), and the reaction mixture was heated at 60 °C for 3.75 h. A second batch of bromoacetamide (10.4 mg, 0.0754 mmol) was added and 5 h hours later a third batch of bromoacetamide (8.6 mg) was added, and the reaction mixture was heated for an additional 12 h. It was diluted with MeOH, filtered and submitted to Prep-HPLC to afford the TFA salt of Example 185 as an off-white solid (37.9 mg).

25 **Example 186:**

E_t₃N (30 uL, 0.215 mmol) and 1-Methyl-1H-imidazole-4-sulfonyl chloride (20.9 mg, 0.1157 mmol) were added into a THF suspension of Example 113 (31.5 mg, 0.0934 mmol), and the reaction mixture was vigorously stirred for 5.75 h. Additional sulfonyl chloride (4.4 mg, 0.0244 mmol) was added and stirring continued for 65 min. The

volatile component was removed *in vacuo*, and the residue was submitted to a Prep-HPLC to afford the TFA salt of Example 186 as an off-white solid (35.5 mg).

Example 187:

5 A mixture of Example 113 (30.4 mg, 0.0901 mmol) and H₂NSO₂NH₂ (38.5 mg, 0.4006 mmol) in dioxane (2.0 mL) was heated at 90 °C for about 19 h. The volatile component was removed *in vacuo* and the residue was submitted to Prep-HPLC to afford Example 187 as an off-white solid (23.4 mg).

10 **Example 188:**

Et₃N (30 uL, 0.215 mmol) was added to a THF (2.0 mL) semi-suspension of Example 113 (30.7 mg, 0.091 mmol), and the mixture was cooled (ice-water) and treated with MeSO₂CH₂SO₂Cl (24.5 mg, 0.127 mmol). The cold bath was removed 1 hr later and stirring was continued for 4.75 h. Additional sulfonyl chloride (54.9 mg, 0.285 mmol) 15 was added and the reaction mixture was stirred for 25.5 h. MeOH was added and the reaction mixture was allowed to stand overnight. All the volatile component was removed *in vacuo* and the crude material was submitted to Prep-HPLC to afford the TFA salt of Example 188. The salt was free-based according to the procedure described for Examples 159-173 to retrieve an off-white solid (4.6 mg).

20

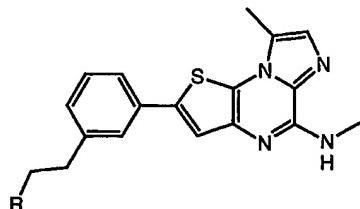
Example 189:

Methyl isocyanate (15 uL, 0.240 mmol) was added into a MeOH (2.0 mL) suspension of Example 113 (29.1 mg, 0.0863 mmol). There was a brief dissolution followed by the formation of heavy suspension. After stirring for 40 min, the suspension 25 was filtered and washed with MeOH to afford Example 189 as an off-white solid (24.1 mg).

Example 190:

Isopropyl isocyanate (40 uL, 0.407 mmol) was added into a MeOH (3.0 mL) 30 suspension of Example 113 (39.0 mg, 0.1156 mmol) and the reaction mixture was stirred

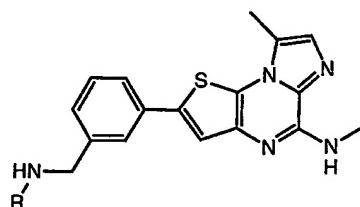
for about 30 min. The precipitate was filtered and washed with MeOH. The solid was submitted to Prep-HPLC purification to afford the TFA salt of Example 190 as an off-white solid (32.7 mg).



5

TABLE 16

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
183		445.08	
184		381.14	
185		452.13	
186		482.06	
187		417.08	
188		494.02	
189		395.18	
190		423.1	

Examples 191-196

5 Examples 191-196 having formula above, wherein R is described in Table 17,
were prepared from the free-base form of Example 118 as follows:

Example 191-192:

Examples 191 and 192 were prepared from Example 118 according the procedure
10 described for the synthesis of 184 and 187, respectively.

Example 193:

Acetic anhydride (11.4 mg, 0.112 mmol) and triethylamine (14.4 mg, 0.142
mmol) were added into a mixture of Example 118 (25 mg, 0.077 mmol) and THF (25
15 mL). The mixture was stirred at 25 °C for 16 h. The volatile component was removed *in*
vacuo and the residue was purified by prep-HPLC to afford the TFA salt of Example 193
as a yellow solid (24.4 mg).

Example 194:

20 Methanesulfonyl chloride (2 mL of 0.0458 M/THF; 0.0916 mmol) and
triethylamine (6 mg, 0.06 mmol) were added to Example 118 (19.7 mg, 0.0609 mmol).
The reaction mixture was stirred at 25 °C for 53.5 h. All the volatile component was
removed *in vacuo*, and the residue was purified by prep-HPLC to afford the TFA salt of
Example 194 as a yellow solid (10.1 mg).

25

Example 195-196:

A mixture of Example 118 (25 mg, 0.077 mmol) and oxalamic acid ethyl ester (90.5 mg, 0.773 mmol) in methanol (10 mL) was refluxed for 17 h. All the volatile component was removed *in vacuo*, and the residue was purified by prep-HPLC to afford the TFA salt of Example 195 (16.4 mg, yellow solid) and the TFA salt of Example 196 (5.9 mg, yellow solid).

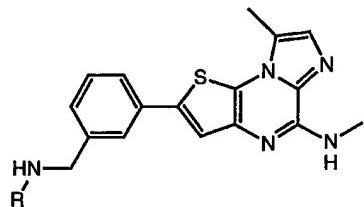
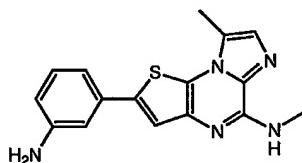


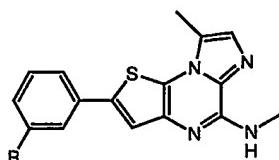
TABLE 17

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
191		367.07	(TFA salt): 7.71 (s, 1H), 7.65 (d, J = 7.9, 1H), 7.61 (br s, 1H), 7.44 (br s, 1H), 7.41 (app t, J = 7.8, 1H), 7.26 (d, J = 7.6, 1H), 6.51 (br m, 1H), 4.24 (br d, J = 4.6, 2H), 3.03 (br s, 3H), 2.74 (s, 3H).
192		403.02	(TFA salt): 7.77 (s, 1H), 7.74 (br s, 1H), 7.67 (d, J = 7.9, 1H), 7.41 (app t, J = 7.8, 1H), 7.39 (s, 1H), 7.33 (d, J = 7.6, 1H), 7.16 (br t, J = 6.1, 1H), 6.71 (br s, 2H), 4.15 (br d, J = 5.5, 2H), 3.00 (br d, J = 3.6, 3H), 2.74 (s, 3H)
193		366.08	(TFA salt): 8.41 (br t, J = 5.7, 1H), 7.72 (s, 1H), 7.66 (d, J = 8.0, 1H), 7.62 (s, 1H), 7.44 (s, 1H), 7.42 (app t, J = 7.7, 1H), 7.25 (d, J = 7.6, 1H),

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
			4.32 (d, J = 6.1, 2H), 3.03 (br s, 3H), 2.74 (s, 3H), 1.90 (s, 3H)
194		402.01	
195		395.07	
196		410.04	

Example 197

Example 197 was prepared from 3-Iodoaniline and stannane 108A according to the procedure described for the synthesis of Example 177. ¹H NMR: 7.54 (s, 1H), 7.43 (q, J = 4.6, 1H), 7.35 (s, 1H), 7.09 (t, J = 7.8, 1H), 6.93 (app d, J = 7.6, 1H), 6.90 (app t, J = 2.0, 1H), 6.55 (dd, J = 8.0, 1.6, 1H), 5.26 (br s, 2H), 2.99 (d, J = 4.9, 3H), 2.72 (br s, 3H). (ESI) m/z (M+H)⁺ = 310.11.

Example 198-201

Examples 198-201 having formula above, wherein R is shown in Table 18, were prepared from the free-base form of Example 197 as follows:

Example 198:

5 Acetoxyacetyl chloride (2 mL of 0.07M/THF, 0.14 mmol) and triethylamine (26.2 mg, 0.259 mmol) were added to Example 197 (40.0 mg, 0.129 mmol). The reaction mixture was stirred at 25 °C for 14h, filtered and washed with THF (1 mL). The filtrate was concentrated *in vacuo*, and a silica gel mesh of the residue was submitted to flash chromatography (EtOAc) to afford a light yellow solid (22.4 mg).

10 Potassium carbonate (18.6 mg, 0.135 mmol) was added to a mixture of the above solid (21.4 mg, 0.0523 mmol) and methanol/DMF (2.0/1.0 mL). The reaction mixture was stirred at 25° C for 15.5 h. The volatile component was removed *in vacuo* and the residue was purified by prep-HPLC to afford the TFA salt of Example 198 as an off-white solid (16.4 mg).

15

Example 199:

Example 197 (30.6 mg, 0.0989 mmol) was added to ethyl isocyanate (2 mL of 0.07M/CH₂Cl₂, 0.14 mmol), and the reaction mixture was stirred at 25 °C for 7.5h. Additional ethyl isocyanate (200 uL 0.07M/CH₂Cl₂, 0.014 mmol) was added and the 20 reaction was stirred for 88.5h. All the volatile component was removed *in vacuo* and the residue was purified by prep-HPLC to afford the TFA salt of Example 199 as a tan solid (30.1 mg).

Example 200 and 201:

25 Ethanesulfonyl chloride (2 mL of 0.07M/CH₂Cl₂, 0.14 mmol) and triethylamine (14.7 mg, 0.145 mmol) were added to Example 197 (31.5 mg, 0.102 mmol), and the mixture was stirred at 25 °C for 5h. The volatile component was removed *in vacuo* and the residue was purified by prep-HPLC to afford the TFA salt of Example 200 (10.9 mg, yellow solid) and the TFA salt of Example 201 (11.5 mg, yellow solid).

30

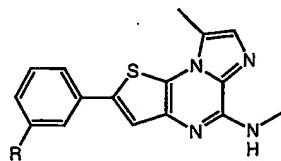
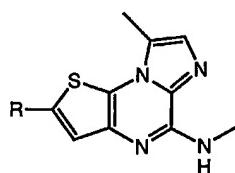


TABLE 18

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
198		368.05	
199		381.07	
200		401.97	
201		493.88	

5

Examples 202-241

- Examples 202-241, having formula shown above, were prepared from stannane
10 108A following the coupling procedure described above for Example 177, using the
desired coupling partners (see, e.g., Preparations 1-75 or commercially available
sources). The resultant products were purified with flash chromatography, Prep-HPLC
and/or recrystallization and were obtained as free-bases or TFA salts.

15

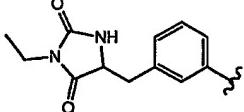
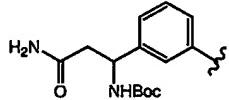
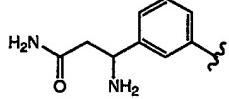
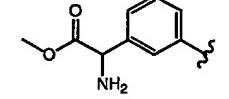
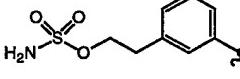
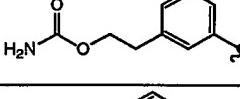
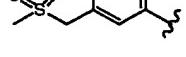
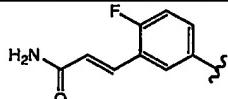
TABLE 19

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
202		374.17	
203		348.10	(Free base): 7.78 (s, 1H), 7.71 (m, 1H), 7.66 (m, 1H), 7.46 (m, 1H), 7.41 (app t, J = 7.8, 1H), 7.36 (d, J = 0.6, 1H), 7.28 (app d, J = 7.6, 1H), 2.99 (d, J = 4.6, 3H), 2.97-2.88 (m, 4H), 2.74 (s, 3H).
204		407.13	
205		413.12	
206		413.12	
207		399.16	
208		395.15	
209		395.15	
210		409.18	

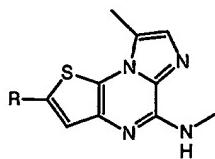
Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
211		409.18	(Free base): 7.76 (s, 1H), 7.68 (br s, 1H), 7.61-7.60 (m, 2H), 7.47 (m, 1H), 7.38-7.35 (m, 2H), 7.20 (d, J = 7.7, 1H), 3.13 (s, 2H), 2.99 (d, J = 4.6, 3H), 2.78 (br s, 4H), 2.73 (s, 3H), 2.58 (d, J = 4.9, 3H).
212		423.19	
213		368.03	(Free base): 8.94 (d, J = 2.3, 1H), 8.43 (d, J = 1.9, 1H), 8.04 (s, 1H), 7.90 (s, 1H), 7.52 (m, 1H), 7.38 (d, J = 0.9, 1H), 3.84 (s, 2H), 3.67 (s, 3H), 2.99 (d, J = 4.8, 3H), 2.74 (d, J = 0.5, 3H).
214		381.21	(Free base): 7.76 (s, 1H), 7.63 (m, 1H), 7.60 (m, 1H), 7.47 (m, 1H), 7.38-7.34 (m, 2H), 7.21 (app d, J = 7.7, 1H), 3.60 (s, 3H), 2.99 (d, J = 4.9, 3H), 2.91 (t, J = 7.6, 2H), 2.73 (d, J = 1.0, 3H), 2.72 (d, J = 7.6, 2H).
215		382.05	
216		393.12	

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
217		435.12	
218		381.08	
219		376.10	(Free base): 8.73 (s, 1H), 8.01 (s, 1H), 7.76 (s, 1H), 7.74 (d, J = 7.9, 1H), 7.71 (s, 1H), 7.48 (q, J = 4.8, 1H), 7.44 (app t, J = 7.7, 1H), 7.36 (s, 1H), 7.22 (d, J = 7.6, 1H), 5.48 (s, 2H), 2.99 (d, J = 4.9, 3H), 2.73 (s, 3H)
220		376.10	
221		407.06	
222		421.10	
223		396.08	
224		381.07	
225		381.06	

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
226		381.06	
227		395.15	
228		409.25	
229		395.22	(TFA salt): 8.38 (br q, J = 4.5, 1H), 8.19 (br d, J = 3.9, 3H), 7.77 (s, 1H), 7.72 (d, J = 8.3, 1H), 7.60 (br s, 1H), 7.43 (app t, J = 7.7, 1H), 7.40 (s, 1H), 7.18 (d, J = 7.6, 1H), 3.98 (br m, 1H), 3.11 (dd, J = 14, 6.1, 1H), 3.03-2.99 (m, 4H), 2.74 (s, 3H), 2.66 (d, J = 4.6, 3H)
230		409.18	
231		409.25	
232		407.23	
233		421.20	(TFA salt): 8.29 (br s, 1H), 7.74 (s, 1H), 7.64 (d, J = 8.0, 1H), 7.57 (br s, 1H), 7.48 (m, 1H), 7.38-7.34 (m, 2H), 7.15 (d, J = 7.7, 1H), 4.44 (m, 1H), 3.07 (dd, J = 14.0, 3.1, 1H),

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
			2.99 (d, J = 4.9, 3H), 2.97 (m, 1H), 2.73 (s, 3H), 2.70 (s, 3H)
234		435.24	
235		481.28	
236		381.20	
237		382.06	
238		418.17	
239		382.22	
240		387.18	(Free base): 7.83 (m, 1H), 7.78 (br s, 1H), 7.77 (m, 1H), 7.51-7.48 (m, 2H), 7.39 (app d, J = 7.7, 1H), 7.37 (br s, 1H), 4.56 (s, 2H), 2.99 (d, J = 4.5, 3H), 2.96 (s, 3H), 2.74 (s, 3H)
241		382.23	

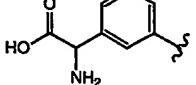
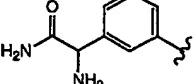
Examples 242-250

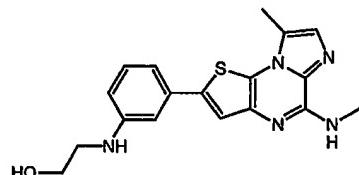


Examples 242-250, having formula shown above, were prepared from the corresponding esters (Example 213 or 214) according to the procedures described for the synthesis of Examples 127, 128 or 131. A number of cases that carry Boc group were deprotected under standard conditions (TFA/CH₂Cl₂).

TABLE 20

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
242		367.19	
243		366.15	
244		354.06	
245		353.08	
246		368.09	
247		368.07	
248		382.04	

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
249		368.09	(TFA salt): 8.81 (br s, 3H), 7.90-7.88 (m, 2H), 7.81 (s, 1H), 7.64 (m, 1H), 7.56 (t, J = 7.8, 1H), 7.46 (d, J = 7.6, 1H), 7.40 (s, 1H), 5.23 (m, 1H), 3.00 (d, J = 3.9, 3H), 2.75 (s, 3H)
250		367.07	(TFA salt): 8.68-8.63(m, 3H), 7.93 (br s, 1H), 7.90 (br s, 1H), 7.88 (d, J = 7.9, 1H), 7.81 (s, 1H), 7.67 (br s, 2H), 7.55 (app t, J = 7.8, 1H), 7.48 (d, J = 7.6, 1H), 7.41 (s, 1H), 4.94 (m, 1H), 3.00 (br d, J = 3.9, 3H), 2.75 (s, 3H)

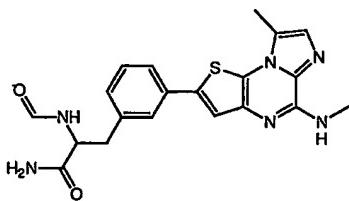
Example 251

5

DIBAL-H (0.27 mL of 1M in CH₂Cl₂, 0.27 mmol) was added to a cooled (0 °C) THF (2.0 mL) suspension of Example 215 (32.1 mg, 0.0842 mmol), the cooling bath was removed, and the reaction mixture was stirred at 25 °C for 22 h. Additional DIBAL-H (50 µL of 1M/CH₂Cl₂, 0.050 mmol) was added at ambient temperature, and the mixture was stirred for another 3 h. It was then quenched with methanol (2 mL) and all the volatile component was removed *in vacuo*. The residue was purified by prep-HPLC to

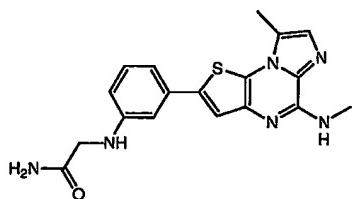
afford the TFA salt of Example 251 as a yellow solid (17.4 mg). (ESI) m/z (M+H)⁺ = 354.12.

5

Example 252

A propylformate (3.0 mL) suspension of Example 224 (46.4 mg, 0.122 mmol) 10 was refluxed for 25 h. The volatile component was removed *in vacuo* and the residue was triturated from MeOH to afford Example 252 as a tan solid (30 mg). (ESI) m/z (M+H)⁺ = 409.18.

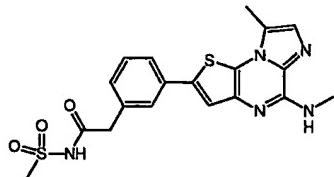
15

Example 253

Trimethylaluminum (0.30 mL of 2M/toluene, 0.60 mmol) was added to a mixture of Example 215 (32.7 mg, 0.0857 mmol) and ammonium chloride (45.0 mg, 0.841 mmol) 20 in 1,4-dioxane (2.0 mL). The reaction mixture was stirred at ambient temperature for 30 min and at 60 °C for 23 h. It was cooled to room temperature and quenched with methanol (2 mL) and stirred for 30 min. The volatile component was removed *in vacuo*, and the residue was purified by prep-HPLC to afford the TFA salt of Example 253 as a

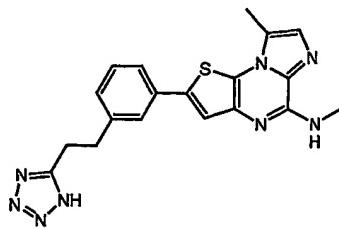
tan solid (12.7 mg). ^1H NMR: 7.59 (s, 1H), 7.45 (br s, 1H), 7.42 (br s, 1H), 7.18 (app t, $J = 8.0$, 1H), 7.13 (br s, 1H), 6.97 (d, $J = 8.5$, 1H), 6.90 (app t, $J = 1.9$, 1H), 6.58 (dd, $J = 8.1, 1.7$, 1H), 3.68 (s, 2H), 3.03 (br s, 3H), 3.73 (s, 3H). (ESI) m/z (M+H) $^+$ = 367.05.

5

Example 254

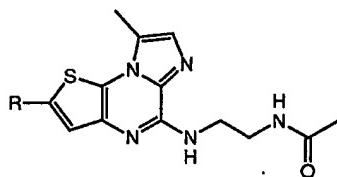
Potassium carbonate (91.8 mg, 0.664 mmol) was added into a 1,4-dioxane (3.0 mL) solution of bromide P75, and the mixture was vigorously stirred for 25 min. Stannane 108A (81.1 mg, 0.213 mmol), LiCl (36.9 mg, 0.870 mmol) and Pd(PPh₃)₄ (12.1 mg, 0.0105 mmol) were sequentially added to the above mixture. The heterogeneous mixture was flushed with N₂ and heated at 90 °C for 19 h. It was allowed to cool to room temperature, the volatile component was removed *in vacuo*, and the residue was submitted to Prep-HPLC to afford a mixture of bromide P75 and the TFA salt of Example 254. The mixture was dissolved in MeOH and loaded onto an SCX column (pre-equilibrated with MeOH), and washed with MeOH; the column was then eluted with 2 N NH₃/MeOH to afford Example 254 as a tan solid (3.1 mg). ^1H -NMR: 7.73 (s, 1H), 7.68 (d, $J = 7.9$, 1H), 7.62 (br s, 1H), 7.47 (q, $J = 4.7$, 1H), 7.39 (app t, $J = 7.8$, 1H), 7.36 (s, 1H), 7.23 (d, $J = 7.6$, 1H), 3.60 (s, 2H), 3.12 (s, 3H), 2.99 (d, $J = 4.6$, 3H), 2.73 (s, 3H). (ESI) m/z (M+H) $^+$ = 430.12.

25

Example 255

A mixture of NaN₃ (118.2 mg, 1.818 mmol) and NH₄Cl (1.731 mmol) was added to a DMF (3.0 mL) solution of Example 203 (56 mg, 0.161 mmol) and the heterogeneous mixture was heated at 110 °C for 68 h. After it cooled to room temperature, it was treated 5 with 0.5 mL water and stirred for 3.5 h. The volatile component was removed *in vacuo* and the crude material was purified with a combination of flash chromatography (0-10% MeOH/EtOAc) and Prep-HPLC to afford the TFA salt of Example 255 as an off-white solid (20.8 mg, 33%). ¹H NMR: 7.72 (s, 1H), 7.61-7.60 (m, 2H), 7.43 (s, 1H), 7.37 (m, 1H), 7.21 (app d, J = 7.6, 1H), 3.28 (t, J = 7.8, 2H), 3.12 (t, J = 7.7, 2H), 3.02 (br s, 3H), 10 2.74 (d, J = 0.6, 3H). (ESI) m/z (M+H)⁺ = 391.10.

Example 256-275

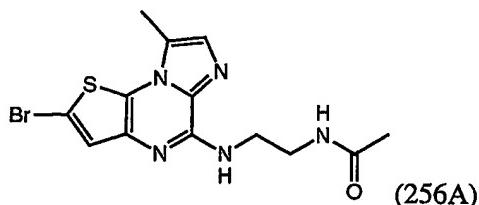


15

Compounds having the formula shown above, wherein R has the values listed in Table 21, were prepared following Steps A-C below.

Step A:

20

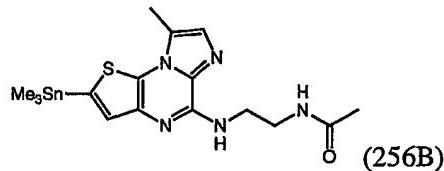


Example 59, which is obtained as a bis TFA salt from a Boc deprotection step, was free-based according to the procedure described in the synthesis of Examples 159-173.

Ac₂O (220 uL, 2.332 mmol) was added drop-wise, over 1 min, to a turbid CH₂Cl₂ (20.0 mL) solution of the free-base form of Example 59 (630 mg, 1.93 mmol) and Et₃N (300 uL, 2.152 mmol). The reaction mixture was stirred for about 4 h and the volatile component was removed *in vacuo*. A silica gel mesh was prepared and submitted to flash chromatography (5-10% MeOH/EtOAc) to afford bromide 256A as an off-white solid (690 mg, >95%). ¹H NMR: 7.99 (br t, J = 5.4, 1H), 7.52 (br t, J = 5.7, 1H), 7.46 (s, 1H), 7.36 (d, J = 0.9, 1H), 3.52 (app q, J = 6.1, 2H), 3.31 (app q, J = 6.1, 2H), 2.64 (s, 3H), 1.8 (s, 3H). (ESI) m/z (M+H)⁺ = 367.95/369.95.

Step B:

15



Bromide 256A (485 mg, 1.317 mmol) and Pd(PPh₃)₄ (41.1 mg, 0.0356 mmol) were added to a 1,4-dioxane (19.5 mL) solution of hexamethylditin (1.627 g, 4.966 mmol) and Et₃N (360 uL, 2.583 mmol). The reaction mixture was heated at 100 °C for 1 h, and was allowed to cool to room temperature. A brown residue was filtered and the filtrate was rotovaped. The residue was triturated with ether (10 mL), and the ash colored suspension was filtered and washed with ether to afford stannane 256B (279 mg, 46.8%). ¹H NMR: 8.00 (br m, 1H), 7.34 (s, 1H), 7.32 (m, 1H), 7.30 (s, 1H), 3.54 (m, 2H), 3.33 (m, 2H), 2.69 (s, 3H), 1.81 (s, 3H), 0.40 (s; staellite peaks with a J = 58.9; 9H). (ESI) m/z (M+H)⁺ = 453.98.

Step C:

Examples 256-275 were prepared from stannane 256B following the coupling procedure described above for Example 177, using the desire coupling partner ((R7)pA-Br or (R7)pA-I) (see, e.g., Preparations 1-75 or commercially available sources). The resultant product was purified with flash chromatography, Prep-HPLC and/or recrystallization and was obtained as a free-base or TFA salt.

5

For Example 272, the Boc group present on the coupling product was deprotected under standard condition (20% TFA/CH₂Cl₂). Example 274 was saponified to afford Example 275 according to the procedure described for the synthesis of Example 127.

10

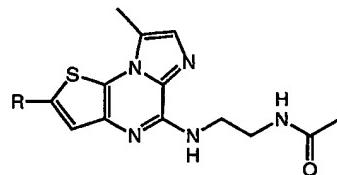
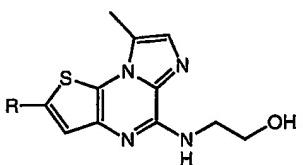


TABLE 21

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
256		384.24	
257		384.19	
258		367.24	
259		368.20	
260		391.21	
261		392.18	(Free base): 9.27 (d, J = 2.5, 1H), 8.95 (d, J = 1.8, 1H), 8.72 (app t, J

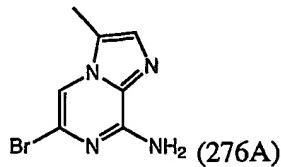
Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
			= 2.2, 1H), 8.04 (s, 1H), 8.01 (br t, J = 5.3, 1H), 7.56 (br t, J = 5.7, 1H), 7.41 (s, 1H), 3.57 (m, 2H), 3.35 (m, 2H), 2.74 (s, 3H), 1.82 (s, 3H).
262		419.21	
263		413.21	
264		456.19	
265		492.16	
266		438.22	
267		474.16	
268		451.09	(TFA salt): 8.02 (br t, J = 5.5, 1H), 7.94 (br t, J = 5.5, 1H), 7.73 (s, 1H), 7.62 (d, J = 7.9, 1H), 7.59 (br s, 1H), 7.42 (d, J = 0.6, 1H), 7.38 (app t, J = 7.7, 1H), 7.20 (d, J = 7.4, 1H), 3.58 (br m, 2H), 3.37-3.30 (m, 4H), 2.77 (m, 2H), 2.75 (s, 3H), 1.82 (s, 3H), 1.80 (s, 3H).
269		487.03	

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
270		452.25	
271		466.28	
272		452.23	
273		422.97	
274		438.01	(Free base): 8.00 (br t, J = 5.5, 1H), 7.72 (s, 1H), 7.70 (app d, J = 8.3, 1H), 7.65 (br s, 1H), 7.46 (br t, J = 5.8, 1H), 7.41 (app t, J = 7.8, 1H), 7.38 (d, J = 0.9, 1H), 7.25 (d, J = 7.7, 1H), 3.77 (s, 2H), 3.64 (s, 3H), 3.57 (m, 2H), 3.35 (m, 2H), 2.74 (s, 3H), 1.82 (s, 3H).
275		424.07	

Example 276-287

5

Step A:



Ammonium hydroxide (10 mL, 29% wt/H₂O) was added into a THF (25.0 mL) solution of Example 1D (5.026g, 20.390 mmol) in a Parr-bomb, the apparatus was
 5 capped and heated at 100 °C until the chloride is completely consumed (>24 h). It was allowed to cool to room temperature, and the precipitate (which was a mixture of white solid and yellow crystals) was filtered and washed with copious water to afford bromide 276 (3.985g). The filtrate was rotovaped, and the residual solid was treated with water, filtered and washed with copious water to retrieve a second batch which has the same
 10 purity as the first one (465 mg; a combined yield of 96.1%). ¹H NMR: 7.80 (s, 1H), 7.33 (br s, 2H), 7.29 (s, 1H), 2.38 (s, 3H). (ESI) m/z (M+H)⁺ = 226.97/228.96.

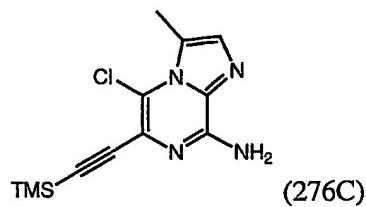
Step B:



15

Bromide 276A (1.016 g) was converted to alkyne 276B following the procedure of Example 1, Step F, except: (a) 30 % less catalyst and co-catalyst were employed; and (b) the column was eluted with 80 % EtOAc/hexanes. Alkyne 276B was retrieved as a light brown solid (1.03 g, 94.2%). ¹H NMR: 7.88 (s, 1H), 7.31 (s, 1H), 7.01 (s, 2H), 2.40
 20 (s, 3H), 0.23 (s, 9H). (ESI) m/z (M+H)⁺ = 245.07.

Step C:



Alkyne 276B (1.016 g) was converted to chloride 276C following the procedure of Example 5, Step C, except: (a) during the aqueous work-up only a single wash was conducted; (b) the column was eluted with 50 % EtOAc/hexanes. Alkyne 276C was retrieved as a fluffy yellow solid (980 mg, 83.4%). ^1H NMR (CDCl_3 , δ) 7.26: 7.27 (s, 1H), 5.51 (br s, 2H), 2.78 (d, J = 1.0, 3H), 0.28 (s, 9H). (ESI) m/z ($\text{M}+\text{H}$) $^+$ = 279.06.

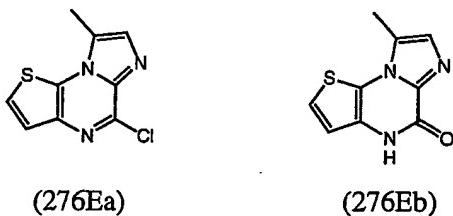
5
Step D:



The cyclization of chloroalkyne 276C (6.36g) to amine 276D was set-up according to the procedure of Example 5, Step D. After all the volatile component was removed *in vacuo*, the residue was treated with 20% MeOH/CHCl₃ (150 mL) and stirred 15 for 15 min. Silica gel was added and the volatile component was removed *in vacuo*; the resultant mesh was submitted to flash chromatography (0-3% MeOH/EtOAc) to afford the cyclized product (276D) as an orangish-brown solid (1.934 g, 41.5%). ^1H NMR: 7.52 (d, J = 5.5, 1H), 7.37 (d, J = 0.7, 1H), 7.19 (d, J = 5.5, 1H), 6.80 (br s, 2H), 2.70 (d, J = 0.6, 3H). (ESI) m/z ($\text{M}+\text{H}$) $^+$ = 205.07.

20

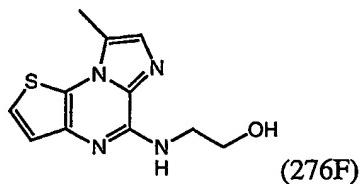
Step E:



An aqueous (11.5 mL) solution of NaNO₂ (4.291 g, 62.19 mmol) was added drop wise over 50 min to a cooled (0 °C) mixture of concentrated HCl (70.0 mL, ~37%) and amine 276D (4.658 g, 22.81 mmol). The reaction mixture was stirred for 5.5 h while allowing the bath to thaw. The bath was then cooled back to 0 °C and the mixture was neutralized with saturated aqueous K₂CO₃ solution. It was diluted with water (160 mL) and extracted with 20% MeOH/CHCl₃, until no more material is extracted. [Note: in the event that a precipitate is formed during extraction, it is filtered and mixed with the final collection of organic extracts]. The combined organic phase was rotovaped, and a silica gel mesh was prepared from the residue and submitted to flash chromatography (1.5-10 % MeOH/CHCl₃) to afford chloride 276Ea (2.545 g, 49.9%) and the hydrolysis byproduct 276Eb (1.84, 39.5 %), both as a light yellow solid. 276Ea: ¹H NMR: 7.83 (d, J = 5.5, 1H), 7.72 (d, J = 0.9, 1H), 7.58 (d, J = 5.8, 1H), 2.81 (d, J = 0.6, 3H). (ESI) m/z (M+H)⁺ = 224.01; 276Eb: ¹H NMR: 11.95 (br s, 1H), 7.56 (d, J = 5.5, 1H), 7.32 (d, J = 0.9, 1H), 7.00 (d, J = 5.8, 1H), 2.63 (d, J = 0.6, 3H). (ESI) m/z (M+H)⁺ = 206.05.

The byproduct 276Eb could be converted to chloride 276Ea as follow. PhNEt₂ (2.9 mL, 18.22 mmol) and POCl₃ (29.0 mL) were added to tricycle 276Eb (2.08 g, 10.13 mmol), and the reaction mixture was refluxed for 26.5 h. The volatile component was removed *in vacuo*, and the residue was partitioned between water and EtOAc. The aqueous phase was neutralized with K₂CO₃ and extracted with EtOAc, until no more compound was coming. The combined organic phase was rotovaped, and a silica gel mesh was prepared from the residue and submitted to flash chromatography (CHCl₃) to afford chloride 276Ea (2.104 g, 92.8%).

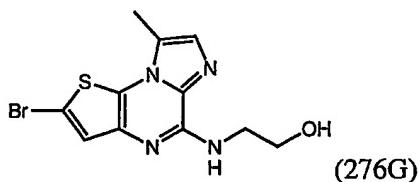
Step F:



Ethanolamine (6.0 mL) was added into a THF (20 mL) solution of chloride 276Ea (979.2 mg, 4.378 mmol) and the reaction mixture was refluxed for 18 h. It was allowed to cool to room temperature and the volatile component was removed *in vacuo*. A silica gel mesh was prepared and submitted to flash chromatography (0-5% MeOH/EtOAc) to retrieve a yellow solid along with oily residue believed to be ethanolamine. The solid was washed with copious ether and EtOAc (6 mL). Alcohol 276F was obtained as a yellow solid (1.005 g, 92.5%). ¹H NMR: 7.52 (d, J = 5.5, 1H), 7.36 (d, J = 0.9, 1H), 7.26 (d, J = 5.5, 1H), 7.13 (br t, J = 5.5, 1H), 4.82 (t, J = 5.3, 1H), 3.63 (m, 2H), 3.56 (m, 2H), 2.69 (d, J = 0.6, 3H). (ESI) m/z (M+H)⁺ = 249.08.

Step G:

15

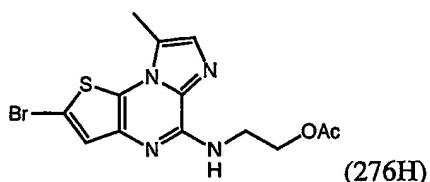


N-Bromosuccinimide (761.7 mg, 4.279 mmol) was added to a cooled (0 °C) THF (50 mL) semi-suspension of alcohol 276F (1.005 g, 4.047 mmol), and the reaction mixture was stirred for 14 h, while allowing the bath to thaw to ~ 11 °C. Silica gel was added to it, and the solvent was removed *in vacuo*. The resultant silica gel mesh was submitted to flash chromatography (0-5 % MeOH/EtOAc) to afford bromide 276G as a yellow solid (1.101g); the sample contained alcohol 276F as an impurity in a ~10:1 mole

ratio (^1H NMR). ^1H NMR: 7.47 (s, 1H), 7.36 (d, J = 1.0, 1H), 7.27 (br m, 1H), 4.79 (t, J = 5.5, 1H), 3.61 (m, 2H), 3.55 (m, 2H), 2.64 (s, 3H). (ESI) m/z (M+H) $^+$ = 326.90/328.90.

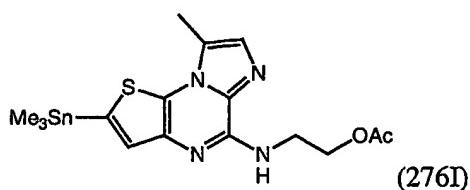
Step H:

5



Et_3N (780 μL , 5.596 mmol), Ac_2O (440 μL , 4.663 mmol) and DMAP (39.7 mg, 0.325 mmol) were added into a THF (30.0 mL) suspension of alcohol 276G prepared above (< 1.100 g, 3.362 mmol). The heterogeneous mixture was stirred for 70 min, and the volatile component was removed *in vacuo*. A silica gel mesh was prepared and submitted to flash chromatography (80% EtOAc/hexanes) to afford bromide 276H as an off-white solid (1.170 g, a 2 steps combined yield of 78.3%). ^1H NMR: 7.62 (br t, J = 5.8, 1H), 7.48 (s, 1H), 7.37 (d, J = 0.9, 1H), 4.23 (t, J = 5.8, 2H), 3.70 (m, 2H), 2.64 (s, 3H), 1.99 (S, 3H). (ESI) m/z (M+H) $^+$ = 368.94/370.94.

Step I:



20

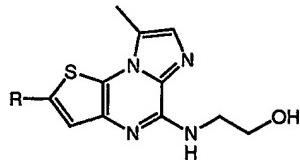
The stannylation of bromide 276H (972.6 mg, 2.634 mmol) was set-up according to the procedure described for compound 69A. After the reaction is over, it was cooled to room temperature, filtered and the filtrate was rotovaped. The oily residue was treated with warm hexanes (50 mL), and swirled briefly and the hexanes was decanted into a

flask and allowed to stand at room temperature. The resulting precipitate was filtered and washed with hexanes to afford stannane 276I as a mixture of light brown solid and crystals (770 mg). ¹H NMR analysis indicates the sample contains minor impurities. ¹H NMR: 7.43 (br t, J = 6.0, 1H), 7.35 (d, J = 0.9, 1H), 7.31 (s, 1H), 4.24 (t, J = 6.0, 2H), 5 3.71 (m, 2H), 2.69 (s, 3H), 2.00 (s, 3H), 0.40 (s; satellite peaks with J = 60.2, 57.6; 9H). (ESI) m/z (M+H)⁺ = 454.88.

Step J:

10 Examples 276-287, having formula shown above and where R is shown in Table 22, were prepared from stannane 276I and the appropriate arylbromides or iodides (see, e.g. Preparations 1-75 or commercially available compounds) according to the coupling procedure described for Example 177, followed by deprotection of the alcohol under standard protocol (K₂CO₃, THF/MeOH). The resultant product was purified with flash 15 chromatography, Prep-HPLC and/or recrystallization and was obtained as a free-base or TFA salt.

Example 286 was saponified to afford Example 287 according to the procedure described for the synthesis of Example 127.

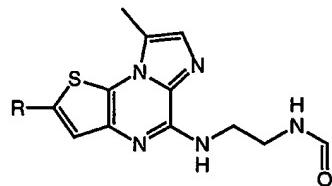


20

TABLE 22

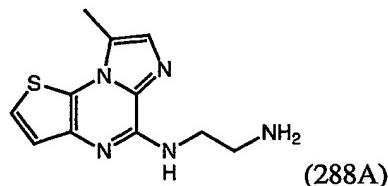
Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
276		410.04	
277		445.98	

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
278		432.98	
279		397.05	
280		410.04	
281		437.08	
282		378.10	
283		411.07	
284		425.22	
285		382.04	
286		397.05	(Free base): 7.74 (s, 1H), 7.70 (br d, J = 8.0, 1H), 7.65 (br s, 1H), 7.41 (app t, J = 7.7, 1H), 7.38 (d, J = 0.9, 1H), 7.26-7.24 (m, 2H), 4.84 (t, J = 5.4, 1H), 3.77 (s, 2H), 3.64 (s, 3H), 3.63 (m, 2H), 3.58 (m, 2H), 2.74 (s, 3H).
287		383.01	

Examples 288-297

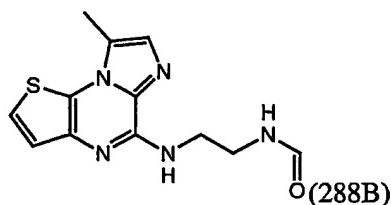
5

Step A:



10 A mixture of chloride 276Ea (1.077 g, 4.815 mmol) and ethylenediamine (70 mL) was stirred at room temperature for about 7 hours. The volatile component was removed *in vacuo* and the resulting semi-solid crude material was submitted to the formylation step below with out purification. (ESI) m/z (M+H)⁺ =248.23

15 Step B:

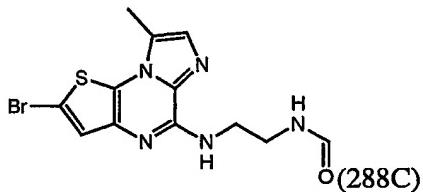


20 Propylformate (22 mL) and Et₃N (800 uL, 5.740 mmol) were added into amine 288A, and the reaction mixture was heated at 80 °C for 19.5 h. It was allowed to cool to

room temperature, silica gel was added and the volatile component was removed *in vacuo*. The resultant mesh was submitted to flash chromatography (5% MeOH/CHCl₃) to afford formamide 288B as a dense dark solid containing noticeable amount of impurity (1.296 g). The material was submitted to the bromination step without further 5 purification. ¹H NMR: 8.14 (br m, 1H), 8.04 (d, J = 1.2, 1H), 7.53 (d, J = 5.5, 1H), 7.39 (br t, J = 5.6, 1H), 7.36 (d, J = 1.0, 1H), 7.26 (d, J = 5.5, 1H), 3.57 (m, 2H), 3.40 (m, 2H), 2.69 (s, 3H). (ESI) m/z (M+H)⁺ = 276.23.

Step C:

10



NBS (864.7 mg, 4.858 mmol) was added in batches over a few min to a cooled (0 °C) THF (100 mL) suspension of impure formamide 288B, and the reaction mixture was 15 stirred for 23 h by allowing the bath to thaw to 13 °C. It was cooled back to 0 °C and two batches of NBS (157.0 mg & 291.3 mg; 2.51 mmol) were added 9 h apart, and the reaction mixture was stirred overnight while allowing the bath to thaw to 15 °C. The volatile component was removed *in vacuo*, and a silica gel mesh was prepared and submitted to flash chromatography (0-3 % MeOH/CHCl₃) to afford bromide 288C as a 20 light yellow solid (1.149 g, 67.4 % combined yield for 3 steps). ¹H NMR: 8.12 (br m, 1H), 8.04 (d, J = 1.5, 1H), 7.54 (br t, J = 5.6, 1H), 7.47 (s, 1H), 7.36 (d, J = 0.9, 1H), 3.54 (m, 2H), 3.38 (m, 2H), 2.63 (s, 3H). (ESI) m/z (M+H)⁺ = 354.10/356.10.

Step D:

25



The stannylation of 288C (1.145 g, 3.232 mmol) was set-up according to the procedure described for compound 69A with the exception that the solvent was increased by 220 %. After the reaction is over, heating was stopped and a few minutes later the mixture was filtered through a filter-paper, and the filtrate was evaporated *in vacuo*. The resultant bi-phasic oil was treated with diethyl ether (25 mL), shaken briefly, and the ether layer was decanted and allowed to stand at room temperature. The precipitate was filtered and washed with ether; stannane 288D was obtained as an ash colored solid containing substantial impurity. The impurity is Me_3SnX origin as is apparent from ^1H NMR analysis. The impure sample was used for the coupling step without further purification. (ESI) m/z ($\text{M}+\text{H}$)⁺ = 440.15.

Step E:

Examples 288-297, having formula shown above where R is described in Table 23, were prepared from stannane 288D and the appropriate arylbromides or iodides (see, e.g. Preparations 1-75 or commercially available compounds) according to the coupling procedure described for Example 177. The resultant product was purified with flash chromatography, Prep-HPLC and/or recrystallization and was obtained as a free-base or TFA salt.

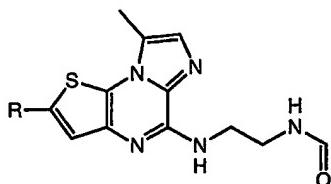
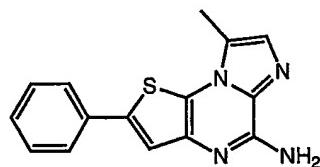


TABLE 23

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
288		388.10	
289		377.16	
290		353.14	
291		353.15	
292		353.15	
293		391.21	
294		405.24	
295		409.25	(Free base; 400 MHZ): 8.14 (br m, 1H), 8.06 (d, J = 1.8, 1H), 7.72 (s, 1H), 7.67 (app d, J = 7.1, 1H), 7.63 (br s, 1H), 7.53 (br s, 1H), 7.48 (app t, J = 5.9, 1H), 7.40-7.36 (m, 2H), 7.24 (d, J = 7.6, 1H), 6.93 (br s, 1H), 3.59 (m, 2H), 3.44 (s, 2H), 3.42 (m, 2H), 2.74 (d, J = 0.7, 3H).
296		423.22	
297		459.23	

Example 298

5

Step A:



10 NBS (284 mg, 1.596 mmol) was added in one batch to a cooled (0 °C) CHCl₃ (13.0 mL) suspension of amine 276D (285 mg, 1.396 mmol), and the reaction mixture was stirred for 19 h while allowing the bath to thaw to room temperature. Two batches of NBS (54.5 mg, 57.4 mg; 0.629 mmol) were added 6 h apart, and the reaction mixture was stirred for an additional 1 h. The volatile component was removed *in vacuo*, and water
15 (10 mL) was added to the residue and vigorously stirred for 30 min. The solid was filtered and washed with copious water. After it was briefly dried, a silica gel mesh was prepared and submitted to flash chromatography (EtOAc) to afford bromide 298A as a light yellow solid (159.9 mg, 40.5%). ¹H NMR: 7.40 (s, 1H), 7.37 (d, J = 0.9, 1H), 6.96 (br s, 2H), 3.32 (s, 3H). (ESI) m/z (M+H)⁺ = 283.02/285.02.

20

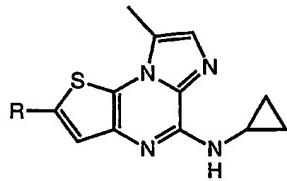
Step B:

LiCl (39.8 mg, 0.918 mmol) and Pd(PPh₃)₄ (10.6 mg, 0.009 mmol) were sequentially added into a mixture of bromide 298A (74 mg, 0.261 mmol), trimethyl(phenyl)tin (201.7 mg, 0.837 mmol) and 1,4-dioxane (3.0 mL). The reaction

mixture was flushed with N₂ and heated at 90 °C for 77 h. After it was allowed to cool to room temperature, the volatile component was removed *in vacuo*. A silica gel mesh was prepared from the residue and submitted to flash chromatography (0-5 % MeOH/EtOAc) to afford a solid, which was carefully washed with a few ml of MeOH to remove colored residues. Example 298 was retrieved as a dull-yellow solid (46.9 mg, 64 %). ¹H NMR: 7.76 (d, J = 7.3, 2H), 7.65 (s, 1H), 7.46 (app t, J = 7.8, 2H), 7.39 (d, J = 0.6, 1H), 7.36 (app t, J = 7.3, 1H), 6.90 (br s, 2H), 2.74 (s, 3H). (ESI) m/z (M+H)⁺ = 281.11.

Example 299-302

10



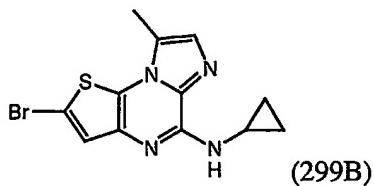
Step A:



15

NBS (82.1 mg, 0.461 mmol) was added in one batch to a THF (3.0 mL) solution of chloride 276Ea (52.7 mg, 0.2356 mmol) and the reaction mixture was stirred in a diffused light for about 21 h. Silica gel was added and the volatile component was removed *in vacuo*, and the resulting silica gel mesh was submitted to flash chromatography (40 % EtOAc/hexanes) to isolate bromochloride 299, contaminated with chloride 276Ea, as an orange solid (52.5 mg, ~ 73%). ¹H NMR (400 MHZ): 7.86 (s, 1H), 7.73 (s, 1H), 2.76 (S, 3H). (ESI) m/z (M+H)⁺ = 303.89.

Step B:



A cyclopropyl amine (5.0 mL) suspension of bromochloride 299A (120 mg, 0.397 mmol) was refluxed for 16 hours. The reaction mixture was cooled to room temperature 5 and the volatile component was removed *in vacuo*. A silica gel mesh was prepared and submitted to flash chromatography to afford bromide 299B as a light yellow solid (102 mg, 79.6%). ^1H NMR: 7.63 (d, $J = 3.7$, 1H), 7.52 (s, 1H), 7.34 (d, $J = 0.9$, 1H), 2.93 (m, 1H), 2.64 (s, 3H), 0.74-0.64 (m, 4H). (ESI) m/z ($\text{M}+\text{H}$) $^+ = 323.06/325.06$.

10 Step C:

Examples 299-302, having formula shown above where R is described in Table 24, were prepared from stannane 299B and the appropriate arylhalide (see, e.g. Preparations 1-75) according to the coupling procedure described for the synthesis of Example 177.

15

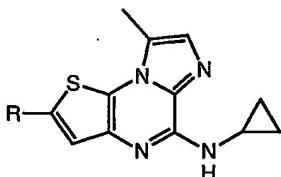
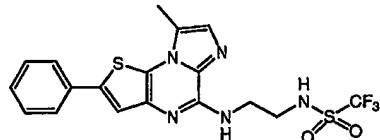


TABLE 24

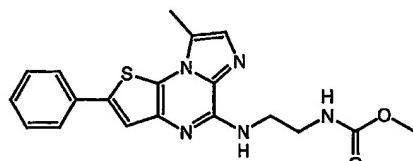
Ex. #	R	$(\text{M}+\text{H})^+$	Other Data (^1H NMR)
299		392.17	(TFA salt; 400 MHZ): 8.42 (br t, $J = 5.9$, 1H), 7.79 (s, 1H), 7.69 (d, $J = 7.9$, 1H), 7.64 (s, 1H), 7.43 (app t, $J = 7.7$, 1H), 7.27 (d, $J = 7.2$, 1H), 4.33 (d, $J = 6.1$, 2H), 2.94 (m, 1H), 2.76 (s, 3H), 1.91 (s, 3H), 0.86 (m,

Ex. #	R	(M+H) ⁺	Other Data (¹ H NMR)
			2H), 0.77 (m, 2H).
300		410.14	
301		428.19	
302		446.16	

Example 303

5

Trifluoromethanesulfonyl chloride (1 mL of 0.093 M in THF, 0.093 mmol) was added drop-wise to a cooled, -40 °C, mixture of Example 5 (30.2 mg, 0.0934 mmol, free-base form) and triethylamine (13 µL, 0.093 mmol) in THF (1 mL). The reaction mixture was allowed to warm up to room temperature over 16 h. The volatile component was removed *in vacuo* and the residue was purified by prep-HPLC to afford the TFA salt of Example 303 as an off-white solid (28.5 mg).

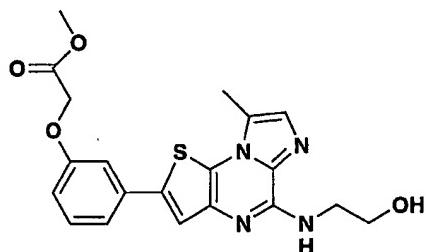
Example 304

15

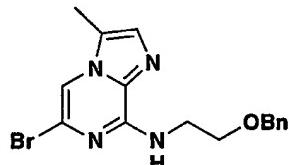
Methyl chloroformate (1.0 mL of 0.124 M in THF, 0.124 mmol) was added to a cooled (0 °C) mixture of Example 5 (39.6 mg, 0.122 mmol; free-base form) and triethylamine (17 µL, 0.122 mmol) in THF (1 mL). The reaction mixture was allowed to 5 warm up to room temperature over 8 h. All the volatile component was removed *in vacuo* and the residue was purified by prep-HPLC to afford the TFA salt of Example 304 as an off-white solid (25.8 mg).

Example 305

10



Step A:



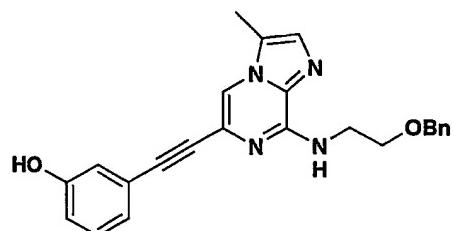
(305A)

15

Preparation 79 (460mg, 3.04 mmol) was added into a THF (5ml) solution of chloride from *Example 1, Step 1D* (500mg, 2.03 mmol) and triethyl amine (1.35ml, 9.69 mmol) in a pressure tube. The reaction mixture was stirred at 65 °C for 21 h. The reaction mixture was cooled to rt and solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and washed with water. The organic layer was washed with brine, dried (MgSO_4), filtered and evaporated *in vacuo*. The crude material was submitted to flash chromatography (ethyl acetate/hexane=50/50) to afford pale yellow solid (500mg, 68%).

¹H NMR (DMSO, 400MHZ): 7.80 (s, 1H), 7.76 (s, 1H), 7.28 (m, 6H), 4.52 (s, 2H), 3.65 (s, 4H), 2.39 (d, J=0.6, 3H). (ESI) m/z (M+H)⁺ = 363.18.

Step B:

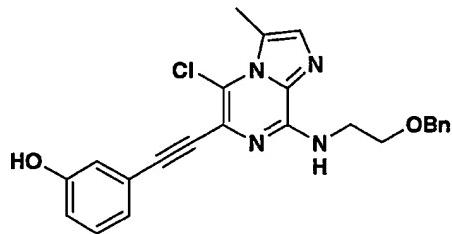


5

(305B)

A mixture of Pd(PPh₃)₄ (65mg, 0.056 mmol) and CuI (10.7mg, 0.056 mmol) was added to
 10 a pressure tube containing a DMF (5ml) solution of bromide 305A (100mg, 0.28 mmol),
 3-ethynyl-phenol (82mg, 0.69 mmol), and TEA (0.16ml, 1.12 mmol). The reaction flask
 was flushed with nitrogen, capped, and heated at 66 °C for 19 h. The reaction mixture
 was then allowed to cool to rt and the precipitate was filtered. The filtrate was exposed to
 vacuum to remove the DMF and the other volatile components. A silica gel mesh was
 15 prepared from the residue and submitted to flash chromatography (50-
 90%EtOAc/hexanes) to afford alkyne 305B as a yellow foam (97mg, 87%). ¹H NMR
 (MeOH, 400MHZ): 7.17 (b, 8H), 6.96 (d, J=7.0, 2H), 6.79 (t, J=4.5, 1H), 4.89 (s, 2H),
 3.71 (d, J=3.6, 2H), 3.68 (d, J=3.6, 2H), 2.31 (s, 3H). (ESI) m/z (M+H)⁺ = 399.12.

20 Step C:



(305C)

5 N-Chlorosuccinimide (32mg, 0.24 mmol) was added to a THF (2.5ml) solution of alkyne
 305B (96mg, 0.24 mmol), and the resulting reaction mixture was heated with an oil bath
 $(50\text{ }^{\circ}\text{C})$ for 21 h. The solvent was removed *in vacuo*, and the residue was dissolved in
 EtOAc and washed with water (2x) and brine. The organic layer was dried (MgSO_4),
 filtered, and evaporated *in vacuo*. The crude material was submitted to flash
 10 chromatography (the sample was loaded onto column with the chloroform solvent; 30%
 EtOAc/hexanes) to afford a clean chloride 305C (66mg, 63%). ^1H NMR (MeOH,
 400MHz): 7.22 (m, 7H), 6.98 (m, 2H), 6.80 (m, 1H), 4.53 (s, 2H), 3.70 (s, 4H), 2.69 (d,
 $J=0.64$, 3H). (ESI) m/z (M+H) $^{+}$ = 433.02.

15 Step D:

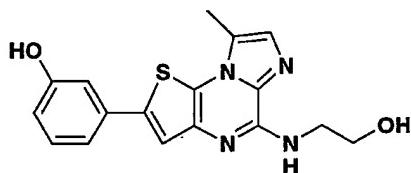


(305D)

DMF (1.5ml) was added to a mixture of chloroalkyne 305C (66mg, 0.15 mmol) and Na₂S·9H₂O (110mg, 0.46 mmol; the solid was crushed with mortar and pestle; 99.99% pure). The resulting heterogeneous reaction mixture was heated for 1hr with an oil bath pre-equilibrated at 100 °C. The reaction mixture was allowed to cool to rt and the volatile component removed *in vacuo*. A silica gel mesh of the residue was prepared and submitted to flash chromatography (50% EtOAc/hexanes) to afford amine 305D as a light yellow solid (40mg, 62%). ¹H NMR (MeOH, 400MHZ): 7.19 (m, 8H), 6.95 (m, 2H), 6.68 (d, J=9.32, 1H), 4.54 (s, 2H), 3.71 (m, 2H), 3.65 (m, 2H), 2.51 (d, J=0.72, 3H). (ESI) m/z (M+H)⁺ = 431.08.

10

Step E:

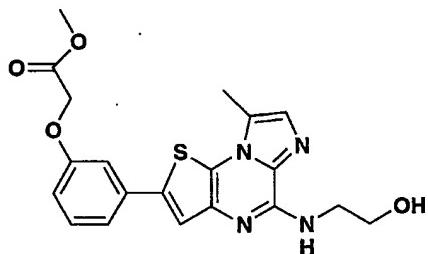


(305E)

15 Boron trifluoride-methyl sulfide complex (4.3ml, 40.5 mmol) was added drop wise to a CH₂Cl₂ (100ml) solution of amine 171D (2.18g, 5.06 mmol) at -78 °C. The reaction mixture was allowed to rise to rt and stirred for 4 h. The solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and washed with PH=7 buffer solution. Sodium bicarbonate was used to neutralize the solution. The organic layer was washed 20 with brine, dried (MgSO₄), filtered and evaporated *in vacuo*. A silica gel mesh of the residue was prepared and submitted to flash chromatography (90% EtOAc/hexanes) to afford ester 305E as a white solid (910mg, 53%). ¹H NMR (MeOH, 400MHZ): 7.50 (d, J=4.1, 2H), 7.27 (t, J=7.8, 1H), 6.68 (m, 1H), 7.11 (t, J=2.0, 1H), 6.82 (m, 1H), 3.89 (t, J=5.2, 2H), 3.77 (t, J=5.2, 2H), 2.80(d, J=0.68, 3H). (ESI) m/z (M+H)⁺ = 341.10.

25

Step F:

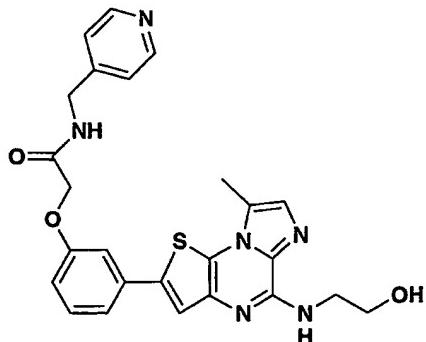


(305F)

5

DMF (12ml) was added to a mixture of bromo-acetic acid methyl ester (83ul, 0.882 mmol), potassium carbonate (325mg, 2.35 mmol) and phenol 171E (200mg, 0.588 mmol). The resulting heterogeneous reaction mixture was stirred for 20 h at rt. The solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and washed 10 with PH=7 buffer solution. The organic layer was washed with brine, dried (MgSO_4), filtered and evaporated *in vacuo*. A silica gel mesh of the residue was prepared and submitted to flash chromatography (30-80% EtOAc/hexanes) to afford ester 305F as a white solid (188mg, 77%). ^1H NMR (MeOH, 500MHZ): 7.46 (d, $J=5.8$, 2H), 7.33 (t, $J=8.0$, 1H), 7.26 (m, 1H), 7.19 (t, $J=2.1$, 1H), 6.91 (m, 1H), 4.86 (s, 2H), 3.89 (t, $J=5.3$, 15 2H), 3.81 (s, 3H), 3.76 (t, $J=5.3, 2H$), 2.74 (d, $J=0.6$, 3H). (ESI) m/z ($\text{M}+\text{H}$)⁺ = 413.04.

Example 306



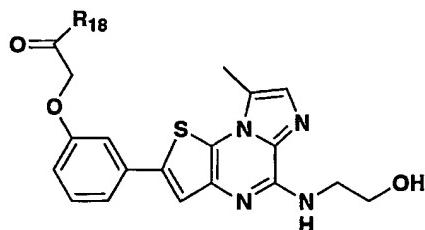
THF (1ml) was added to a mixture of ester 305F (18.9mg, 0.0458 mmol) and C-Pyridin-4-yl-methylamine (13mg, 0.137 mmol). After replaced with nitrogen, AlMe₃ (69ul, 0.137 mmol) was added slowly. Large amount of gas was produced. The reaction mixture was stirred for 20 h at rt. 1N HCl was added to neutralize the solution. Small amount of 1N NaOH was used to adjust to PH=8. Solvent was removed *in vacuo*. Prep HPLC was used to purify the residue to obtain white solid (9.3mg, 43%). ¹H NMR (MeOH, 400MHZ): 8.66 (d, J=7.4, 2H), 8.31 (d, J=7.4, 2H), 7.58 (s, 1H), 7.52 (d, J=0.88, 1H), 7.37 (m, 3H), 7.07 (m, 1H), 4.91 (s, 2H), 3.90 (t, J=5.3, 2H), 3.79 (t, J=5.3, 2H), 2.79 (t, J=3.4, 3H).
 (ESI) m/z (M+H)⁺ = 489.11.

Examples 307-347

The compounds shown below in Table 25 were synthesized using the methods described in Example 306 and commercially available amines.

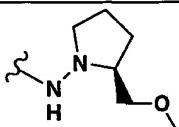
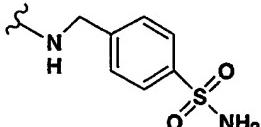
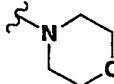
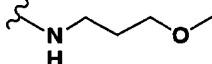
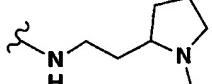
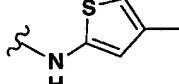
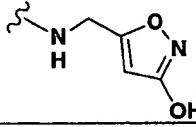
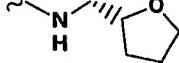
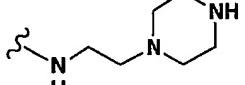
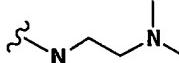
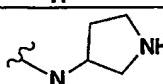
15

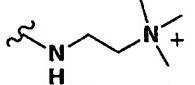
Table 25

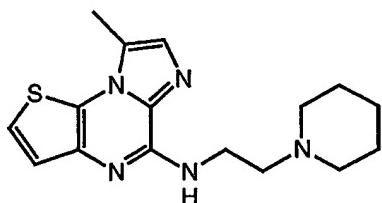


Ex. #	R ₁₈	(M+H) ⁺	¹ H NMR (MeOH, 400MHz)
307		523.19	
308		489.17	
309		475.16	
310		489.17	(TFA salt): 8.62 (d, J=5.0, 1H), 8.16 (t, J=3.9, 1H), 7.65 (m, 2H), 7.58 (s, 1H), 7.52 (d, J=0.84, 1H), 7.39 (m, 3H), 7.06 (m, 1H), 4.73 (s, 4H), 3.90 (t, J=5.3, 2H), 3.79 (t, J=5.3, 2H), 2.81 (s, 3H)
311		466.07	
312		482.11	(TFA salt): 8.18 (b, 1H), 7.48 (t, J=3.8, 2H), 7.36 (m, 3H), 6.98(m, 1H), 4.54 (s, 2H), 3.89 (t, J=5.4, 2H), 3.77 (t, J=5.4, 2H), 2.76 (d, J=0.68, 3H), 1.47 (t, J=8.3, 4H), 0.93 (d, J=8.5, 9H)
313		482.19	
314		482.12	
315		438.06	
316		495.04	
317		452.07	
318		470.05	

319		456.06	
320		483.25	
321		482.19	
322		438.19	
323		454.06	
324		452.06	
325		440.08	
326		442.04	
327		454.06	
328		511.09	(TFA salt): 7.58 (s, 1H), 7.53 (d, J=0.8, 1H), 7.34 (m, 3H), 7.04 (m, 1H), 4.64 (s, 2H), 4.04 (b, 2H), 3.98 (m, 2H), 3.92 (t, J=5.3, 2H), 3.80 (t, J=5.3, 3H), 3.72 (b, 6H), 3.10 (m, 2H), 3.79 (d, J=0.68, 3H)
329		492.08	
330		454.06	
331		452.06	
332		470.08	
333		483.02	

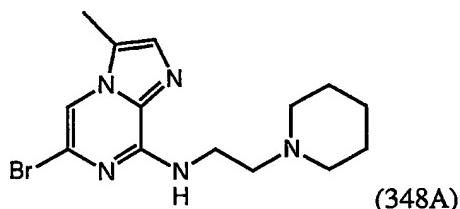
334		511.29	
335		567.15	
336		468.06	
337		470.05	
338		470.07	
339		454.07	
340		509.10	
341		494.98	
342		494.98	
343		482.02	
344		510.06	
345		469.18	
346		466.99	

347		483.03	
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Example 348

5

Step A:

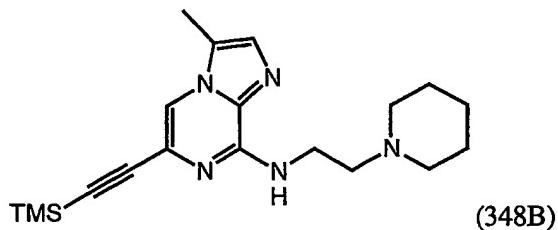


Example 1D (5.00 g, 20.28 mmol) was added to a THF (37.0 ml) solution of 1-(2-aminoethyl) piperidine (3.01 g, 23.50 mmol) and triethylamine (6.0 ml, 39.22 mmol).

- 10 The reaction mixture was heated with an oil bath (~ 65 °C) for 17 h, cooled to room temperature and the precipitate was filtered. Silica gel was added to the filtrate and evaporated in vacuo . The resulting silica gel mesh was submitted to flash chromatography (50-70 % EtOAc/hexane) to afford bromide compound 348A as an off-white solid (6.17 g, 90 % yield). m/z ($M+H$)⁺ = 339

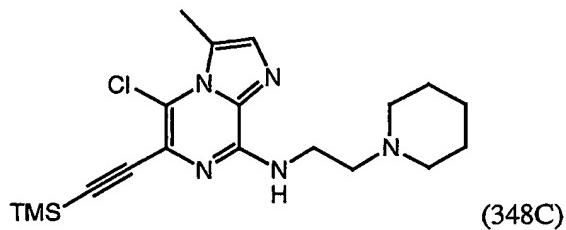
15

Step B:



A mixture of $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.94 g, 0.8112 mmol) and CuI (0.31 g, 1.622 mmol) was added to a pressure tube containing a DMF (50 ml) solution of bromide 348A (6.86 g, 20.28 mmol), (trimethylsilyl)acetylene (6.49 ml, 45.63 mmol) and triethylamine (11.31 ml, 81.12 mmol). The reaction flask was flushed with nitrogen, capped and heated at 64 °C for ~ 3 h. The reaction mixture was then allowed cooling to room temperature and the precipitate was filtered. The filtrate was exposed to vacuum to remove the DMF and other volatile components. The residue was washed with ether. A silica gel mesh was prepared from the residue and submitted to flash chromatography (50-80 % EtOAc/hexane) to afford alkyne 348B as a yellow foam (5.90 g, 82% yield). m/z (M+H)⁺ = 356

Step C:



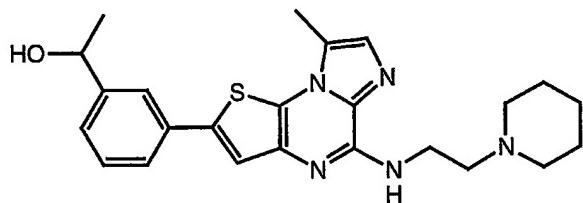
N-Chlorosuccinimide (2.45 g, 18.39 mmol) was added to a THF (80 ml) solution of alkyne 348B (5.44g, 15.32), and the resulting reaction mixture was heated with an oil bath (~ 60 °C) for 8 h. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 and washed with water (2x) and brine. The organic layer was dried (MgSO_4), filtered and evaporated in vacuo. The crude material was submitted to flash chromatography (90 % $\text{CHCl}_3/\text{MeOH}$) to afford a clean chloride 348C (4.78g, 80% yield) m/z (M+H)⁺ =391.

Step D:

DMF (18.0 ml) was added to a mixture of chloroalkyne 348C (1.00 g, 2.56 mmol) and $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ (1.93 g, 8.03 mmol); the solid was crushed with mortar and pestle; 99.99 % pure), and the resulting heterogeneous reaction mixture was heated for 1 hour with an

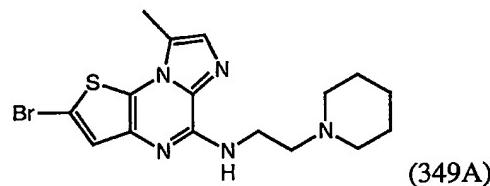
oil bath pre-equilibrated at 100 °C. The reaction mixture was allowed to cool to room temperature and all the volatile component was removed in vacuo. A silica gel mesh of the residue was prepared and submitted to flash chromatography (50~100% EtOAc/hexane) to afford the title compound as a light yellow solid (0.36 g, ~ 45 %). m/z 5 $(M+H)^+ = 316.$

Example 349



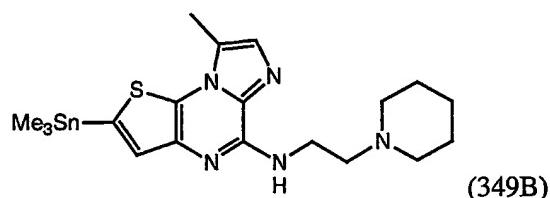
10

Step A:



15

N-Bromosuccinimide (373 mg, 2.10 mmol) was added in batches over 3 min to a cooled (ice-water) THF (12.0 ml) semi-solution of amine 348D (617 mg, 1.96 mmol). The reaction mixture was stirred for 17 h while allowing the bath to thaw. After removing the solvent in vacuo, the resultant solid residue was dissolved in CHCl₃ (pre-washed with 20 NaHCO₃ solution) and washed with water (3X) and brine. It was dried (MgSO₄), filtered and evaporated in vacuo. A silica gel mesh of the crude material was prepared and submitted to flash chromatography (50-100 % EtOAc/hexane) to afford bromide 349A as an off-white fluffy solid (618mg, ~ 80 % yield). m/z $(M+H)^+ = 394/396.$

Step B:

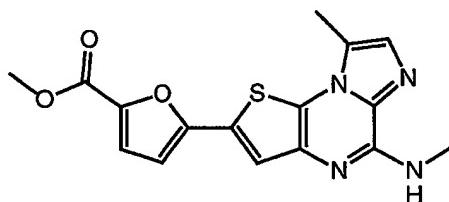
5 A toluene (10 ml) solution of hexamethylditin (1.149g, 3.51 mmol) was treated
with bromide 349A (378mg, 0.959mmol) and triethylamine (0.27mL, 1.919 mmol). After
nitrogen was bubbled through the mixture for 5 min, $\text{Pd}(\text{Ph}_3\text{P})_4$ (38.0mg, 0.033mmol)
was added. The reaction mixture was heated with a 100 °C oil bath for 35 min. The dark
reaction mixture was cooled to room temperature, filtered through a pad of Celite,
10 washed with EtOAc, and the filtrate was evaporated in vacuo. The residue was triturated
with ether, and the light brown solid was filtered and washed with copious ether and
dried in vacuo (344mg of stannane 349B was retrieved). LC/MS analysis of the sample
indicated that it contains minor impurities including amine 348D. $m/z (\text{M}+\text{H})^+ = 479$

15 **Step C**

Stannane 349B (54.4 mg, ~ 0.1138 mmol), 3-bromo-alpha-methylbenzyl alcohol (45.7mg, 0.2276mmol), PdCl₂(Ph₃P)₂ (7.99mg, 0.0114 mmol), KF (15.1 mg, 0.2603 mmol) and DMF (2.0 ml) were sequentially added into a vial. Nitrogen was 5 bubbled through the heterogeneous reaction mixture for about a minute, and it was lowered into a 90 °C oil bath and heated for at least 6 h. When the stannane is completely consumed, the DMF was removed in vacuo, and the crude material was purified with a PREP HPLC to afford the title compound (125mg, 60%). m/z (M+H)⁺ =436.

10

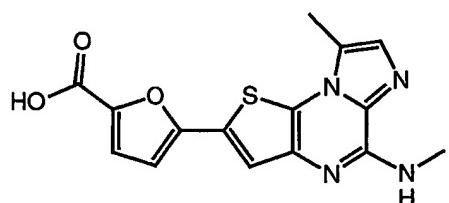
Example 350



15

Stannane 108A (160 mg, ~ 0.4199 mmol), methyl 5-bromo-2-furoate (258.3mg, 1.2598mmol), PdCl₂(Ph₃P)₂ (28.9mg, 0.0412 mmol), KF (50.6 mg, 0.8704 mmol) and DMF (5.2 mL) were sequentially added into a vial. Nitrogen was bubbled through the heterogeneous reaction mixture for about a minute, and it was lowered 20 into a 90 °C oil bath and heated for at least 6 h. When the stannane is completely consumed, the mixture was filtered, washed with DMF and the resultant title product was purified with PREP-HPLC (86mg, 60%). m/z (M+H)⁺ = 343.1.

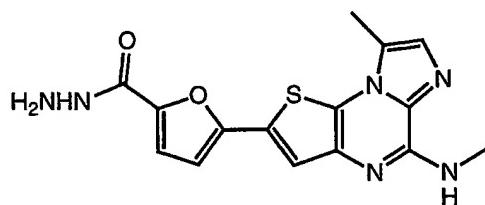
Example 351



25

Example 350 (25mg, 0.0731mmol) was treated with 1N NaOH (0.73ml, 0.731mmol). The reaction mixture was put in a sonicator for 1hr and the resultant title product was purified with PREP-HPLC (25mg, 78%). m/z (M+H)⁺ = 329.

Example 352

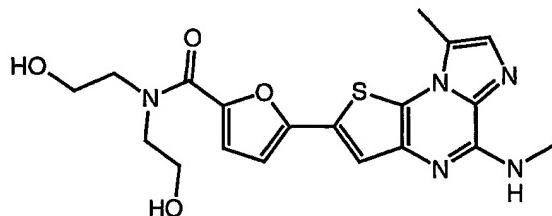


10

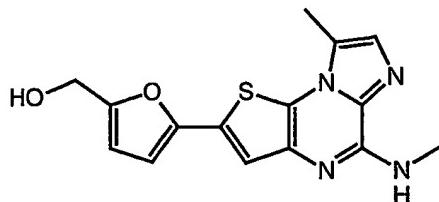
The mixture of Example 350 (20mg, 0.058mmol) and hydrazine (18.6mg, 0.58mmol) in EtOH (1.0ml)/DMSO (1.0ml) was heated in an oil bath at 90 °C for 2 h. The resultant title product was purified with PREP-HPLC. Yield is 15mg, 76%. m/z (M+H)⁺ = 343.

15

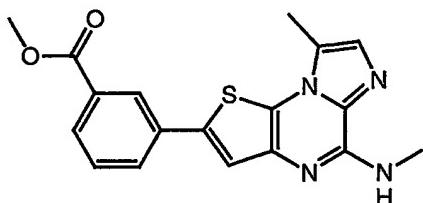
Example 353



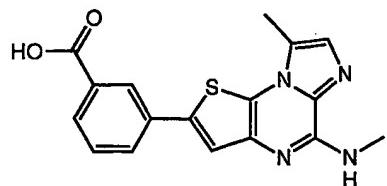
The mixture of Example 350 (20mg, 0.058mmol) and diethanolamine (60.9mg, 0.58mmol) in EtOH (1.0ml)/DMSO (1.0ml) was heated in an oil bath at 90°C overnight. The resultant title product was purified with PREP-HPLC. Yield is 17mg, 70%. m/z (M+H)⁺ = 416.

Example 354

Stannane 108A (80 mg, ~ 0.210 mmol), 5-bromo-2-furylmethylalcohol (111mg, 0.630mmol), PdCl₂(Ph₃P)₂ (14.4mg, 0.021 mmol), KF (25.3 mg, 0.435 mmol) and DMF (3.0 ml) were sequentially added into a vial. Nitrogen was bubbled through the heterogeneous reaction mixture for about a minute, and it was lowered into a 90 °C oil bath and heated for 16 h. When the stannane is completely consumed, the mixture was filtered, washed with DMF and the resultant title product was purified with PREP-HPLC. Yield is 42.8mg, 65%. m/z (M+H)⁺ = 315.

Example 355

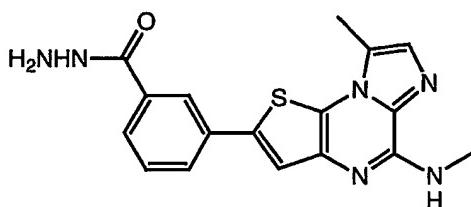
15 Stannane 108A (160 mg, ~ 0.4199 mmol), methyl 3-bromobenzoate (270.9mg, 1.2598mmol), PdCl₂(Ph₃P)₂ (28.9mg, 0.0412 mmol), KF (50.6 mg, 0.8704 mmol) and DMF (5.2 ml) were sequentially added into a vial. Nitrogen was bubbled through the heterogeneous reaction mixture for about a minute, and it was lowered into a 90 °C oil bath and heated for 16 h. When the stannane is completely consumed, the mixture was filtered, washed with DMF and the filtered solid contained desired title product (purity: 90 %). Yield is 118mg, 80%. ¹H NMR (DMSO, δ= 2.50 ppm; 500 MHZ) 8.19 (m, 1H), 8.10 (app d, J=7.5, 1H), 7.92 (app d, J=7.5, 1H), 7.85 (s,1H), 7.62 (app t, J=7.5, 1H), 7.40 (m, 1H), 7.39(m, 1H), 3.91 (s, 3H), 3.00 (d, J= 4, 3H), 2.74 (s, 3H).
20
25 m/z (M+H)⁺ = 353.1.

Example 356

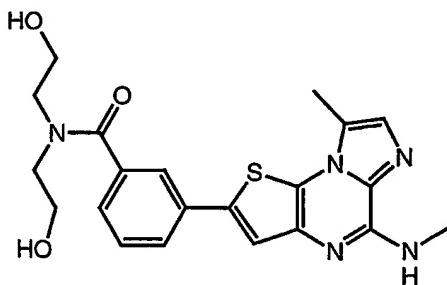
5 Example 355 (20mg, 0.057mmol) was treated with 1N NaOH (0.57ml, 0.57mmol). The reaction mixture was put in a sonicator for 1hr and the resultant title product was purified with PREP-HPLC. Yield is 15.4mg, 80%. m/z (M+H)⁺ = 339.

Example 357

10



A mixture of Example 355 (20mg, 0.057mmol) and hydrazine (18.2mg, 0.57mmol) in EtOH (1.0ml)/DMSO (1.0ml) was heated in an oil bath at 90°C for 2 h.
15 The resultant title product was purified with PREP-HPLC. Yield is 15.6mg, 78%. m/z (M+H)⁺ = 353.

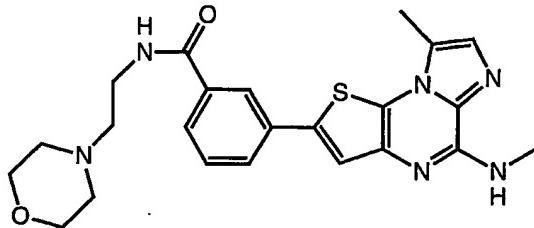
Example 358

20

A mixture of Example 355 (20mg, 0.057mmol) and diethanolamine (59.9mg, 0.57mmol) in DMSO (2.0ml) was heated in an oil bath at 90°C overnight. The resultant title product was purified with PREP-HPLC. Yield is 18mg, 75%. m/z (M+H)⁺ = 426.

5

Example 359

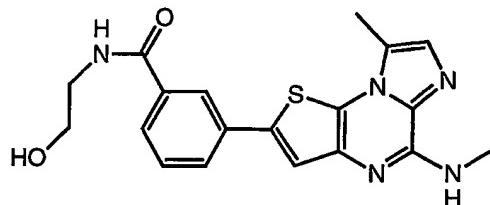


10 A mixture of Example 355 (20mg, 0.057mmol) and N-(2-aminoethyl)-morpholine (74.1mg, 0.57mmol) in DMSO (2.0ml) was heated in an oil bath at 90 °C for 2days. The resultant title product was purified with PREP-HPLC. Yield is 19mg, 74%. ¹H NMR (DMSO, δ= 2.50 ppm; 500 MHZ): 9.00 (app t, J = 5.0, 1H), 8.34 (m, 1H), 8.12 (app d, J=7.5, 1H), 7.99 (s, 1H), 7.98 (app d, J=7.5, 1H), 7.74 (app t, J=7.5, 1H), 7.71 (m, 1H), 7.53 (m, 1H), 3.33-3.90 (m, 8H), 3.22 (m, 2H), 3.04 (m, 2H), 3.14 (d, J= 2.5, 3H), 2.89 (s, 3H). m/z (M+H)⁺ = 451.1.

15

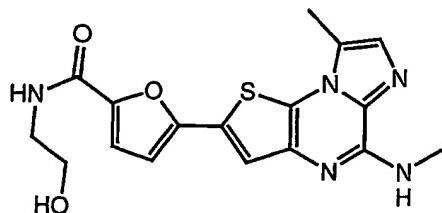
20 A mixture of Example 355 (20mg, 0.057mmol) and N-(2-aminoethyl)-morpholine (74.1mg, 0.57mmol) in DMSO (2.0ml) was heated in an oil bath at 90 °C for 2days. The resultant title product was purified with PREP-HPLC. Yield is 19mg, 74%. ¹H NMR (DMSO, δ= 2.50 ppm; 500 MHZ): 9.00 (app t, J = 5.0, 1H), 8.34 (m, 1H), 8.12 (app d, J=7.5, 1H), 7.99 (s, 1H), 7.98 (app d, J=7.5, 1H), 7.74 (app t, J=7.5, 1H), 7.71 (m, 1H), 7.53 (m, 1H), 3.33-3.90 (m, 8H), 3.22 (m, 2H), 3.04 (m, 2H), 3.14 (d, J= 2.5, 3H), 2.89 (s, 3H). m/z (M+H)⁺ = 451.1.

Example 360



20

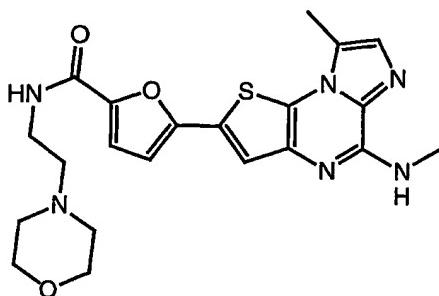
25 A mixture of Example 355 (20mg, 0.057mmol) and 2-aminoethanol (34.8mg, 0.57mmol) in DMSO (2.0ml) was heated in an oil bath at 90 °C for 1h. The resultant title product was purified with PREP-HPLC. Yield is 16.5mg, 76%. m/z (M+H)⁺ = 382.

Example 361

5

A mixture of Example 350 (20mg, 0.058mmol) and 2-aminoethanol (36.4mg, 0.58mmol) in DMSO (2.0ml) was heated in an oil bath at 90°C for 1 h. The resultant title product was purified with PREP-HPLC. Yield is 16.6mg, 77%. m/z (M+H)⁺ = 372.

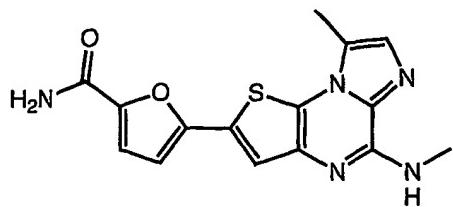
10

Example 362

- A mixture of Example 350 (20mg, 0.058mmol) and N-(2-aminoethyl)-
15 morpholine (75.4mg, 0.58 mmol) in DMSO (2.0ml) was heated in an oil bath at 90 °C
for 2 days. The resultant title product was purified with PREP-HPLC. Yield is 18.9
mg, 74%. ¹H NMR (DMSO, δ= 2.50 ppm; 500 MHZ): 8.67 (app t, J = 5.5, 1H), 7.84
(s, 1H), 7.39 (s, 1H), 7.25 (d, J = 4.0, 1H), 7.07 (d, J = 3.5, 1H), 3.80-3.33 (m, 8H),
3.20 (m, 2H), 3.00 (m, 2H), 2.99 (m, 3H), 2.73 (s, 3H). m/z (M+H)⁺ = 441.1.

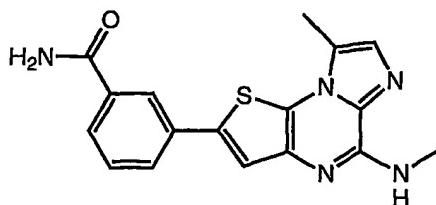
20

Example 363



A mixture of Example 350 (20mg, 0.058mmol) and NH₄OH (~30% in H₂O, 4.0ml) in DMSO (1.0 ml) was heated at 90 °C in a pressure tube for 4 h. The resultant title product was purified with PREP-HPLC. Yield is 14.6mg, 77%. m/z (M+H)⁺ = 328.

Example 364

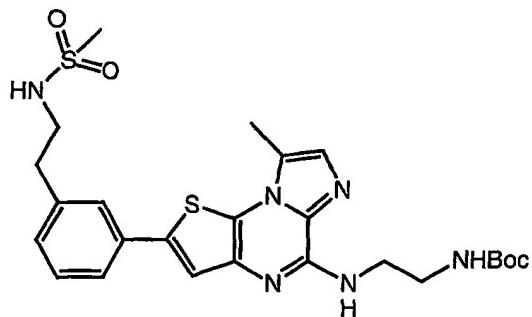


10

A mixture of Example 355 (20mg, 0.057mmol) and NH₄OH (~30% in H₂O, 4.0ml) in DMSO (1.0ml) was heated at 90 °C in a pressure tube for 4 h. The resultant title product was purified with PREP-HPLC. Yield is 15mg, 78%. m/z (M+H)⁺ = 338.

15

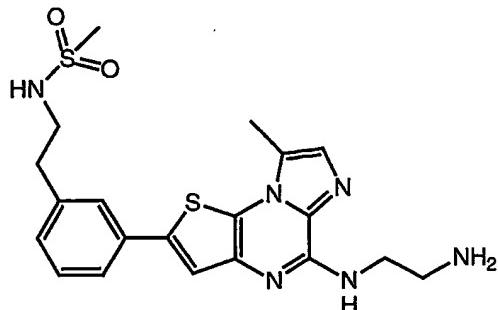
Example 365



A dioxane (6.0 ml) solution of Example 69A (200mg, 0.392mmol) and
20 Preparation 29 (227mg, 0.816mmol.) was degassed with nitrogen and treated with

Pd(*Ph*₃P)₄ (16.9 mg, 0.0146 mmol) and LiCl (57.1mg, 1.347 mmol). The reaction mixture was stirred at 90 °C for 4 h, cooled to room temperature, diluted with EtOAc, and evaporated onto silica gel. The resulting silica gel mesh was submitted to standard flash chromatography (60-75% EtOAc/Hexane) to isolate the title compound as a white solid (149mg, 70%). m/z (M+H)⁺ = 545.

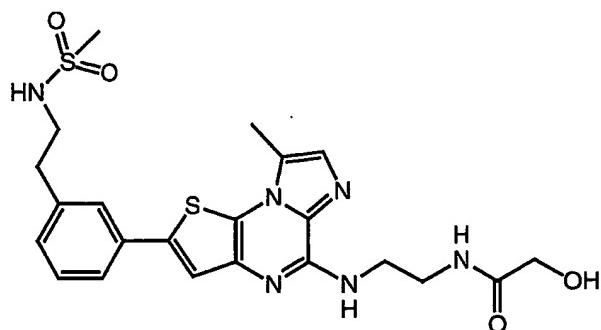
Example 366



Example 365 (200 mg, 0.376 mmol) was treated with 20 % TFA/CH₂Cl₂ (12 ml) in an ice bath, and then the reaction mixture was stirred at room temperature for 4 h. The volatile component was removed in vacuo, and the residue was triturated with Ether and the resulting crude solid was purified on a PREP-HPLC to afford the TFA salt of the title compound (146mg, 90%). m/z (M+H)⁺ = 445.

15

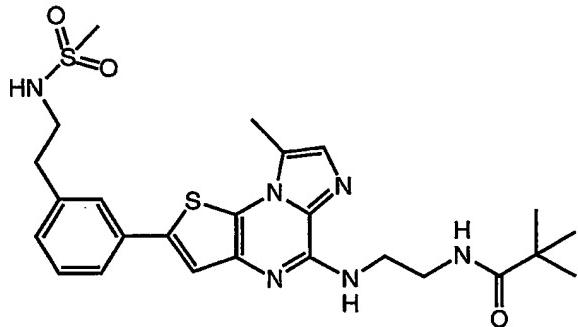
Example 367



A solution of ethyl chloroformate (10.7mg, 0.0986 mmol) in THF (1ml) was added dropwise at -5 °C to a solution glycolic acid (6.8 mg, 0.0896 mmol) and N,N-diisopropylethylamine (12.7mg, 0.0986 mmol) in THF (1ml). The reaction mixture was stirred. At -5 °C for 40 min and then a solution of Example 366 (TFA salt, 50

mg, 0.0896 mmol) in THF (1ml) was added. After stirring at 0 °C for 4 h, the reaction mixture was poured into brine. The resulting mixture was extracted with ethyl acetate twice. The combined extracts were washed with water (2 x), dried over MgSO₄ and the solvent was evaporated. The resulting title compound was purified on 5 a PREP-HPLC (33.7mg, 75%). m/z (M+H)⁺ = 503.

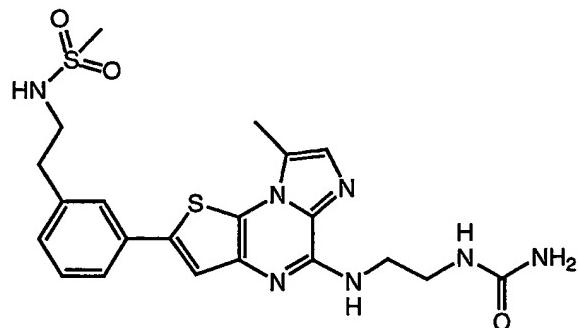
Example 368



10 NaHCO₃ (15.1mg, 0.18mmol) was added to a mixture of Example 366 (TFA salt, 25.1mg, 0.045mmol) in EtOH (1ml)/ H₂O (1ml). The reaction mixture was stirred for 20mins and then trimethylacetyl chloride (5.43 mg, 0.045 mmol) was added. The reaction mixture was heated at 60 °C overnight. The resulting crude title product was purified on a PREP-HPLC (17.6mg, 74%). m/z (M+H)⁺ = 529.

15

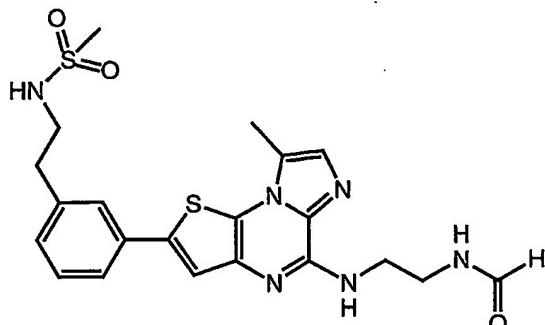
Example 369



A mixture of Example 366 (TFA salt, 70 mg, 0.125 mmol) and trimethylsilyl 20 isocyanate (85%, 51 mg, 0.0376 mmol) in THF (5.0ml) was stirred at 65 °C in a

sealed tube for 18 h. The resulting title product was purified on a PREP-HPLC (48.1mg, 79%). m/z (M+H)⁺ = 488.

Example 370

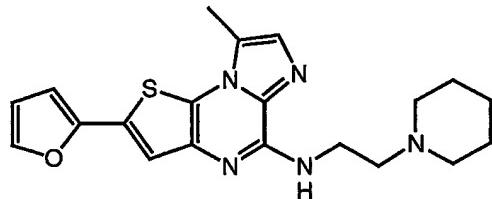


5

A mixture of Example 366 (100 mg, 0.225 mmol) and ethyl formate (50 mg, 0.676 mmol) in THF (5.0ml) was stirred at 65 °C in a sealed tube for 12 h. The resulting title product was purified on a PREP-HPLC (82.8mg, 78%). m/z (M+H)⁺ = 473.

10

Example 371



15

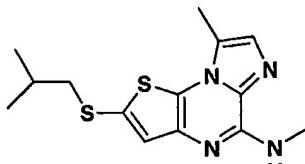
Bromide 349A (100.0 mg, ~ 0.254 mmol), 2-(tributylstannyly)furan (200.6 mg, 0.562 mmol), PdCl₂(Ph₃P)₂ (37.9 mg, 0.054 mmol), KF (57.2 mg, 0.985 mmol) and DMF (3.2 ml) were sequentially added into a vial. Nitrogen was bubbled through the heterogeneous reaction mixture for about a minute, and it was lowered into a 100 °C oil bath and heated for 16 h. DMF was removed in vacuo. Redissolved in EtOAc and washed with water, brine, dried over MgSO₄ and concentrated. The resultant title product (dark brown) was purified with PREP-HPLC (59mg, 61%). ¹H NMR (DMSO, δ= 2.50 ppm; 500 MHZ) 7.79 (br t, J = 5.6, 1H), 7.77 (d, J = 1.5, 1H), 7.49

20

(s, 1H), 7.43 (m, 1H), 6.94 (d, J = 3.5, 1H), 6.65 (dd, J = 3.5, 1.5, 1H), 3.86 (app q, J = 6.0, 2H), 3.63 (m, 2H), 3.40 (m, 2H), 2.95 (m, 2H), 2.73 (s, 3H), 1.83 (m, 2H), 1.64 (m, 3H), 1.41 (m, 1H). m/z (M+H)⁺ = 382.1.

Example 372

5



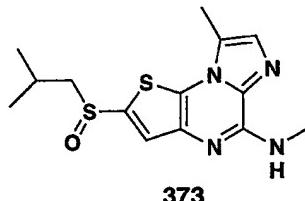
372

A solution of N-(2-bromo-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-amine (0.050 g, 0.168 mmol) in N,N-dimethylformamide (4 mL) was treated with 2-methyl-1-propanethiol (150 μ L, 2.0 mmol) and potassium hydroxide (0.038 g, 0.67 mmol). The mixture was heated at 85°C overnight in a sealed tube, then diluted with ethyl acetate, washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate and the residue was purified on preparative HPLC (acetonitrile/ water/ ammonium acetate) to yield Compound 372 (0.014g, 28%).

15 1 H NMR (CDCl₃, 400 MHz) δ : 7.46 (1H, q, J=4.6 Hz), 7.38 (1H, s), 7.34 (1H, s), 2.96 (3H, d, J=4.6 Hz), 2.81 (2H, d, J=7.1 Hz), 2.66 (3H, s), 1.81 (1H, m), 1.00 (6H, d, J=7.1 Hz). LRMS (ESI, m/z, M+H⁺) 306.

Example 373

20

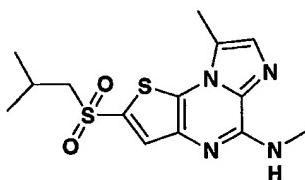


373

A solution of N-(2-(2-methylpropylthio)-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-amine (0.005 g, 0.016 mmol) in dichloromethane (3 mL) was treated with peracetic acid (0.1 M in acetic acid, 0.195 mL, 0.019 mmol) at -15°C. The

reaction was allowed to slowly reach room temperature for 5 hours and then quenched with dimethylsulfide (1M solution in methanol). The solvents were evaporated to give Compound 373 (0.0045 g, 90%) as a white solid. NMR (DMSO-d₆, 400 MHz) δ: 7.81 (1H, s), 7.70 (1H, br s), 7.41 (1H, s), 3.12 (1H, m), 2.99 (3H, d, J=3.4 Hz), 2.95 (1H, m), 2.73 (3H, s), 2.04 (1H, m), 1.07 (3H, d, J=6.5 Hz), 1.06 (3H, d, J=6.6 Hz).
 5 LRMS (ESI, m/z, M+H⁺) 323.

Example 374

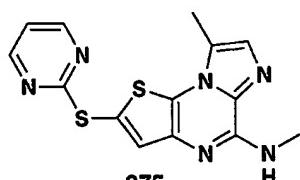


10

374

A solution of N-(2-(2-methylpropylthio)-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-amine (0.003 g, 0.010 mmol) in dichloromethane (3 mL) was treated with peracetic acid (0.1 M in acetic acid, 0.190 mL, 0.019 mmol) at room
 15 temperature. The mixture was stirred overnight then peracetic acid (0.190 mL, 0.019 mmol) was added and the mixture was refluxed. The reaction was quenched with dimethylsulfide (1M solution in methanol) and the solvents were evaporated to give Compound 374 (0.003 g, quantitative) as an off-white solid. NMR (DMSO-d₆, 400 MHz) δ: 7.97 (1H, s), 7.75 (1H, q, J=4.5 Hz), 7.43 (1H, s), 3.44 (2H, d, J=6.1 Hz),
 20 2.99 (3H, d, J=4.5 Hz), 2.72 (3H, s), 2.10 (1H, m), 1.02 (6H, d, J=7.2 Hz). LRMS (ESI, m/z, M+H⁺) 339.

Example 375



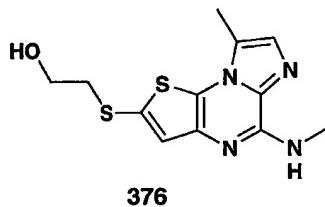
25

375

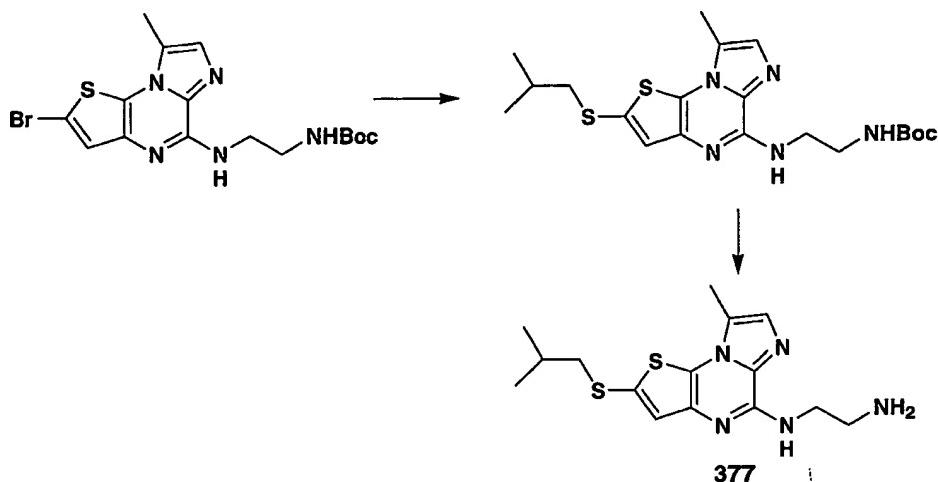
A solution of tris(dibenzylideneacetone)-dipalladium(0) (0.010 g) and bis[(2-diphenylphosphino)phenyl]ether (0.010 g) in toluene (6 mL) was bubbled with argon for 3 minutes. N-(2-Bromo-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-
 5 amine (0.020 g, 0.067 mmol) was added followed by 2-mercaptopypyrimidine (0.011 g, 0.1 mmol) and potassium tert-butoxide (1.0M solution in tetrahydrofuran, 0.1 mL, 0.1 mmol). The mixture was heated under reflux for 2 hours. The mixture was filtered over celite and the solvent was evaporated. The residue was purified by Prep HPLC to give Compound 375 (0.004 g, 18%) as a white solid. ¹H NMR (DMSO-d₆, 400
 10 MHz) δ: 8.68 (2H, d, J=4.6 Hz), 7.62 (1H, s), 7.54 (1H, br q), 7.39 (1H, s), 7.33 (1H, t, J=4.6 Hz), 2.98 (3H, d, J=4.7 Hz), 2.68 (3H, s). LRMS (ESI, m/z, M+H⁺) 329.

Example 376

15



A solution of N-(2-bromo-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-
 20 amine (0.025 g, 0.0841 mmol) in N,N-dimethylformamide (3 mL) was treated with 2-hydroxyethanethiol (15 μL, 0.168 mmol), potassium hydroxide (0.009 g, 0.168 mmol) and copper(I) oxide (0.012g, 0.0841 mmol). The mixture was heated at 85°C for 3 hours in a sealed tube, then diluted with ethyl acetate, washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate and the residue was purified on preparative HPLC (acetonitrile/ water/ ammonium acetate) to yield
 25 Compound 376 (0.005g, 20%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.45 (1H, s), 7.27 (1H, s), 5.98 (1H, m), 3.83 (2H, t, J=6.2 Hz), 3.80 (1H, t, J=6.1 Hz), 3.19 (3H, d, J=5.1 Hz), 3.04 (2H, t, J=6.1 Hz), 2.72 (3H, s). LRMS (ESI, m/z, M+H⁺) 295.

Example 377

5 N-(2-Bromo-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-(2-tert-butoxycarbonylaminoethyl)-amine (0.010 g, 0.023 mmol) was reacted as described in Example 1 to afford N-(2-(methylpropylthio)-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-(2-tert-butoxycarbonylaminoethyl)-amine (0.004 g, 40%). This compound was then stirred in a solution of dichloromethane/trifluoroacetic acid (8:2, 10 3 mL) at room temperature for 3 hours. The solvents were evaporated to give Compound 377 as a brown solid (0.003 g, 61%, 2 TFA salts). NMR (DMSO-d₆, 400 MHz) δ: 7.77 (2H, br s), 7.67 (1H, t, J=5.5 Hz), 7.41 (1H, s), 7.37 (1H, s), 3.72 (2H, q, J=5.9 Hz), 3.11 (2H, m), 2.83 (2H, d, J=6.5 Hz), 2.68 (3H, s), 1.81 (1H, m), 1.00 (6H, d, J=6.6 Hz). LRMS (ESI, m/z, M+H⁺) 336.

15

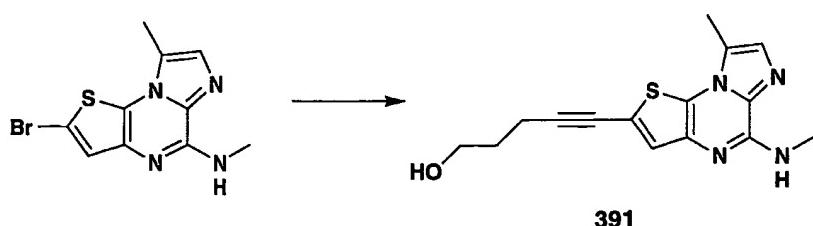
The following examples were prepared as described in Example 377.



Ex	R	HPLC Ret. time (min.) _a	Purity %	MS (e/z) (M+H) ⁺

378	SCH(CH ₃) ₂	1.69	100	322
379	SCH ₂ CH(OH)CH ₂ OH	1.13	100	354
380		1.65	100	360
381	S(CH ₂) ₄ CH ₃	2.14	100	350
382		1.8	96.3	386
383	SCH ₂ CH(CH ₃)CH ₂ CH ₃	2.05	100	350
384	SCH ₂ CH ₂ CH(CH ₃) ₂	2.09	100	350
385		2.28	100	384
386		2.27	100	384
387		2.07	100	348
388		2.09	100	370
389		1.51	91.3	371
390	SCH ₂ CH ₂ NH ₂	1.38	81.8	323

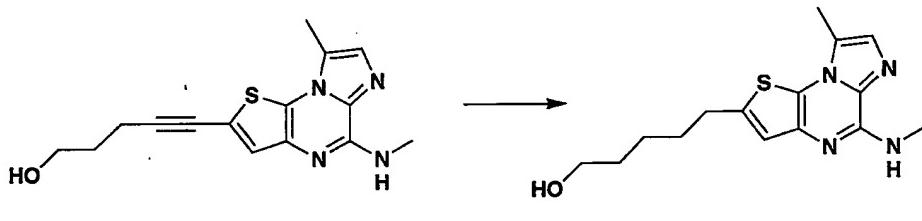
^aHPLC conditions used to determine retention times; 2 min gradient 0-100% B in A;
 (A; 5mM NH₄OAc in 90/10 water/acetonitrile; B; 5mM NH₄OAc in 10/90
 water/acetonitrile) using a Primesphere C-18 4.6x30 mm column at 254 nm

Example 391

A solution of N-(2-bromo-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-amine (0.050 g, 0.168 mmol) (0.050 g, 0.168 mmol) in N,N-dimethylformamide (3 mL) was added copper(I) iodide (15 mgs), triethylamine (0.1 mL) and 5-hydroxy-pentyne (0.392 μ L, 4.2 mmol). Argon was bubbled in the solution, then palladium(II) 5 triphenylphosphine (15 mgs) was added and the mixture was stirred at 80°C for 4 hours. The mixture was filtered on celite and the solvent was evaporated. The residue was purified by Prep HPLC to give Compound 391 (0.044g, 88%).
¹H NMR (DMSO-d₆, 400 MHz) δ : 7.49 (1H, q, J=4.5 Hz), 7.36 (1H, s), 7.35 (1H, s), 4.56 (1H, br t), 3.52 (2H, br q), 2.97 (3H, d, J=4.5 Hz), 2.66 (3H, s), 2.55 (2H, t, J=7.1 10 Hz), 1.71 (2H, m). LRMS (ESI, m/z, M+H⁺) 301.

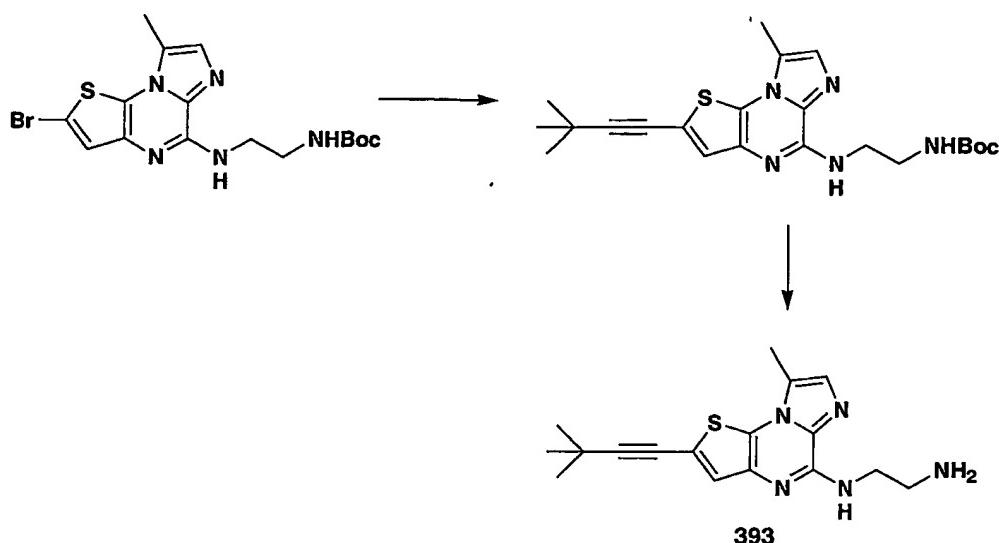
Example 392

15



A solution of N-(2-(hydroxy-pentyn-5-yl)-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-amine (0.015 g, 0.05 mmol) in ethanol (10 mL) was hydrogenated (Parr, 15 psi) in presence of 10% Pd/C. The mixture was stirred for 2.5 hours, then filtered 20 on Celite and washed with ethanol and dichloromethane/methanol (9:1). The solvents were evaporated and the residue was purified by Prep HPLC to give Compound 392 (5 mgs, 33%). ¹H NMR (DMSO-d₆, 400 MHz) δ : 7.31 (1H, s), 7.29 (1H, m), 7.02 (1H, s), 4.35 (1H, t, J=5.0 Hz), 3.40 (2H, m), 2.96 (3H, d, J=4.5 Hz), 2.86 (2H, t, J=7.4 Hz), 2.66 (3H, s), 1.68 (2H, m), 1.49-1.36 (4H, m). LRMS (ESI, m/z, M+H⁺) 25 305.

Example 393

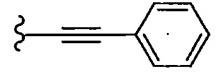
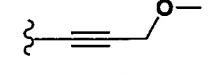
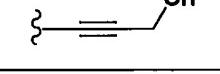


A solution of N-(2-bromo-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-(2-tert-butoxycarbonylaminoethyl)-amine (0.030 g, 0.070 mmol) in N,N-dimethylformamide (1 mL) was added copper(I) iodide (10.5 mgs), triethylamine (0.05 mL) and 2,2-dimethyl-but-3-yne (200 μ L, 3.65 mmol). Argon was bubbled in the solution, then palladium(II) triphenylphosphine (13.8 mgs) was added and the mixture was stirred at 80°C for 2 hours. The mixture was filtered on celite and the solvent was evaporated. The residue was purified by silica gel chromatography (50% ethyl acetate in hexane) to give N-(2-hydroxy-pentyn-5-yl)-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-(2-tert-butoxycarbonylaminoethyl)-amine (0.021 g, 70%). This compound was dissolved in dichloromethane (1 mL) and treated with trifluoroacetic acid (0.2 mL) for 45 minutes. The solvents were evaporated and the residue was dissolved in methanol and treated with MP-carbonate resin. This mixture was stirred at room temperature for 2 hours, then filtered. The resin was washed with methanol and the filtrate was evaporated to give Compound 393 (0.014 g, 87%). NMR (DMSO-d₆, 400 MHz) δ : 7.36 (2H, s), 7.27 (1H, s), 7.25 (1H, s), 3.51 (2H, q, J=5.6 Hz), 2.87 (2H, m), 2.65 (3H, s), 1.24 (9H, s). LRMS (ESI, m/z, M+H⁺) 327. HRMS for C₁₇H₂₁N₅S calcd: 327.1518, found: 327.1516.

The following examples were prepared as described in Example 393.



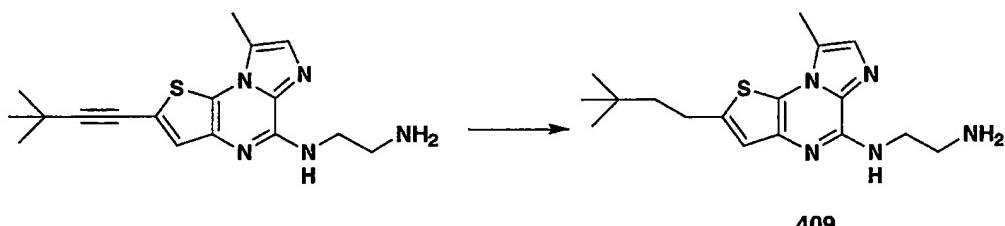
Ex	R	HPLC Ret. time (min.) ^a	Purity %	MS (e/z) (M+H) ⁺
394		2.11	100	378
395		1.73	100	349
396		2.18	100	312
397		1.47	100	328
398		1.36	100	316
399		3.01	97	368
400		2.8	100	354
401		1.84	100	364
402		2.2	100	314
403		1.22	100	330

404		2.11	100	348
405		2.69	100	342
406		2.43	100	348
407		1.65	100	316
408		1.29	100	302

^aHPLC conditions used to determine retention times; 2 min gradient 0-100% B in A; (A; 5mM NH₄OAc in 90/10 water/acetonitrile; B; 5mM NH₄OAc in 10/90 water/acetonitrile) using a Primesphere C-18 4.6x30 mm column at 254 nm

5

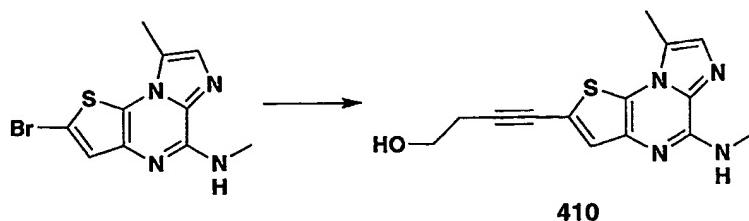
Example 409



- 10 A solution of N-(2-(2,2-Dimethyl-butynyl)-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-(2-aminoethyl)-amine (0.017 g, 0.0519 mmol) in methanol (1 mL) was treated with 10% Pd/C (0.002 g), and stirred under hydrogen for 5 hours. The mixture was filtered on celite and the solvent was evaporated to give Compound 409 (0.004 g, 29%) as a gummy solid. NMR (DMSO-d₆, 400 MHz) δ: 0.96 (9H, s), 1.62 (2H, m), 2.69 (3H, s), 2.85 (2H, m), 3.23 (2H, t, J=5.6 Hz), 3.81 (2H, t, J=5.6 Hz), 6.97 (1H, s), 7.30 (1H, s). LRMS (ESI, m/z, M+H⁺) 332. HRMS for C₁₇H₂₆N₅S calcd: 332.1909, found: 332.1912.
- 15

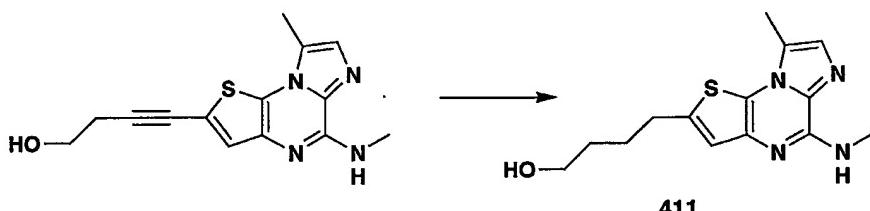
Example 410

20



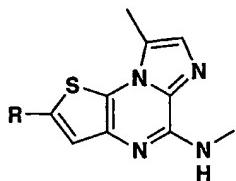
A solution of N-(2-bromo-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-amine (0.040 g, 0.135 mmol) in N,N-dimethylformamide (3 mL) was treated with 3-butyn-1-ol (0.4 mL,), triethylamine (0.1 mL), copper(I) iodide (0.01 g), and tetrakis(triphenylphosphine) palladium(0) (0.01 g). The mixture was stirred at 100°C for 3 hours. The reaction was filtered on celite and the filtrate was evaporated. The residue was purified by prep HPLC to give Compound 410 (0.029 g, 74%). NMR (DMSO-d₆, 400 MHz) δ: 7.49 (1H, q, J=4.7 Hz), 7.35 (2H, s), 4.95 (1H, br t), 3.60 (2H, br qa), 2.97 (3H, d, J=4.7 Hz), 2.66 (3H, s), 2.64 (2H, t, J=6.9 Hz). LRMS (ESI, m/z, M+H⁺) 287.

Example 411

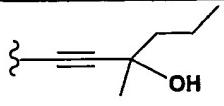
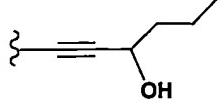
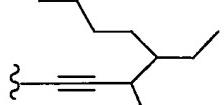
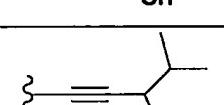
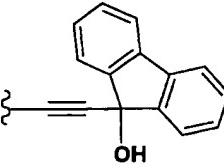
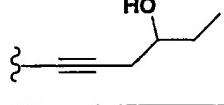
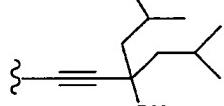
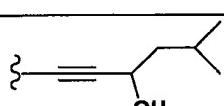
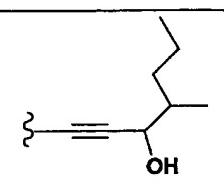
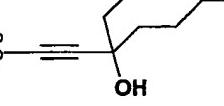
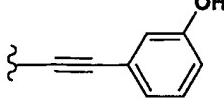


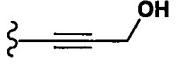
A solution of N-(2-(4-hydroxy-butynyl)-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-amine (0.008 g, 0.028 mmol) in ethanol (5 mL) was treated with 10% Pd/C (0.005 g) and hydrogenated (15 psi) in a Parr hydrogenator. The mixture was filtered on Celite which was then washed with dichloromethane/methanol (1:1). The solvents were evaporated to give Compound 411 (0.004 g, 50%). NMR (DMSO-d₆, 400 MHz) δ: 7.32 (1H, s), 7.31 (1H, qa, J=5.1 Hz), 7.02 (1H, s), 4.41 (1H, t, J=5.2 Hz), 3.45 (2H, q, J=6.3 Hz), 2.95 (3H, d, J=5.1 Hz), 2.87 (2H, t, J=7.4 Hz), 2.66 (3H, s), 1.71 (2H, m), 1.03 (2H, m). LRMS (ESI, m/z, M+H⁺) 291.

The following examples that have been prepared as described in Example 410.



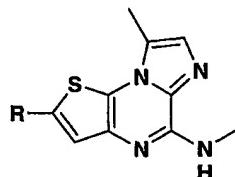
Ex	R	HPLC Ret. time (min.) ^a	Purity %	MS (e/z) (M+H) ⁺
412		1.65	100	327
413		1.51	100	315
414		1.74	100	341
415		1.47	83	301
416		1.38	100	287
417		1.43	91	301
418		1.52	100	301
419		1.87	100	343
420		1.68	100	349.
421		2.45	100	439

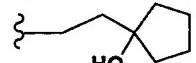
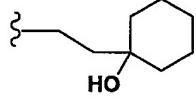
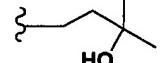
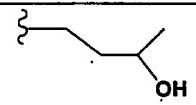
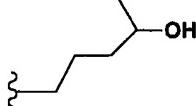
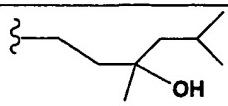
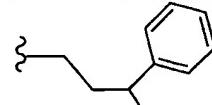
422		1.74	100	329
423		1.66	92	315
424		2.18	100	371
425		1.65	100	315
426		1.92	95	423
427		1.56	100	315
428		2.31	100	385
429		1.77	100	329
430		1.92	100	343
431		2.02	100	357
432		1.78	91	335

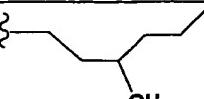
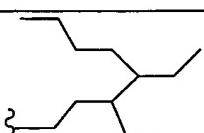
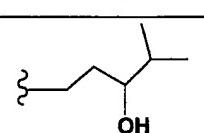
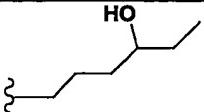
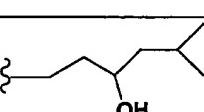
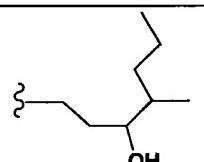
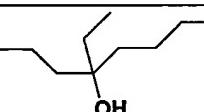
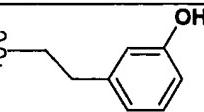
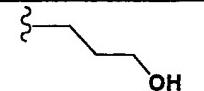
433		1.30	96	273
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^aHPLC conditions used to determine retention times; 2 min gradient 0-100% B in A; (A; 5mM NH₄OAc in 90/10 water/acetonitrile; B; 5mM NH₄OAc in 10/90 water/acetonitrile) using a Primesphere C-18 4.6x30 mm column at 254 nm

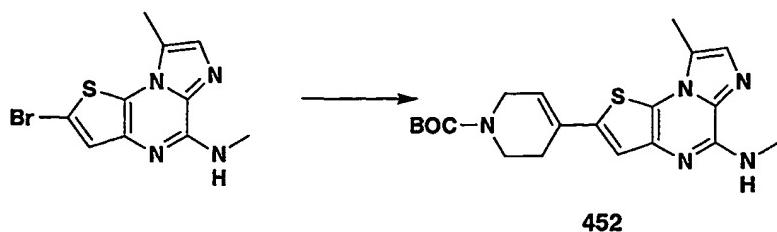
5 The following examples were prepared as described in Example 411.



Ex	R	HPLC Ret. time (min.) ^a	Purity %	MS (e/z) (M+H) ⁺
434		1.61	100	331
435		1.55	100	319
436		1.74	98	345
437		1.41	100	305
438		1.34	100	291
439		1.43	94	305
440		1.82	89	347
441		1.65	96	353

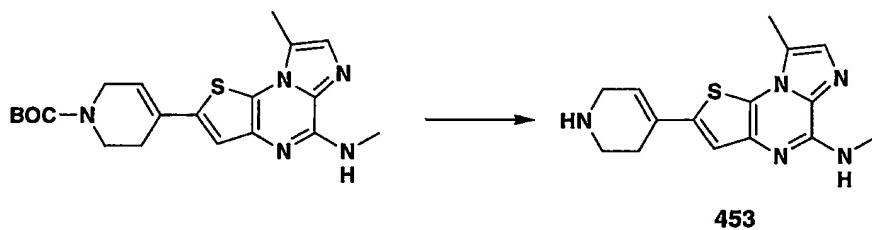
442		1.66	95	333
443		1.6	97	319
444		2.12	86	375
445		1.59	100	319
446		1.55	100	319
447		1.72	99	333
448		1.87	94	347
449		1.95	88	361
450		1.65	81	339
451		1.26	95	277

^aHPLC conditions used to determine retention times; 2 min gradient 0-100% B in A;
 (A; 5mM NH₄OAc in 90/10 water/acetonitrile; B; 5mM NH₄OAc in 10/90
 water/acetonitrile) using a Primesphere C-18 4.6x30 mm column at 254 nm



5 A stirred solution of N-(2-bromo-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-amine (0.050 g, 0.168 mmoles) in N-methylpyrrolidinone (4 mL) was treated with N-Boc-1,2,3,6-tetrahydro-4-tributylstannylpyridine (0.119 g, 0.252 mmol), tris-dibenzylideneacetone dipalladium (10 mgs) and triphenylarsine (15 mgs). The reaction was heated at 90°C overnight and was then diluted with ethyl acetate, washed
10 with water and dried over anhydrous magnesium sulfate. After filtration, the organic phase was evaporated to give a residue which was purified by preparative thin layer chromatography followed by Prep Hplc to give Compound 452 (0.035 g, 52%).
NMR (DMSO-d₆, 400 MHz) δ: 1.44 (9H, s), 2.69 (3H, s), 2.55 (2H, br s), 2.96 (3H, d, J=4.7 Hz), 3.57 (2H, t, J=5.6 Hz), 4.02 (2H, br s), 6.19 (1H, br s), 7.29 (1H, s), 7.34
15 (1H, s), 7.40 (1H, q). LRMS (ESI, m/z, M+H⁺) 399.

Example 453

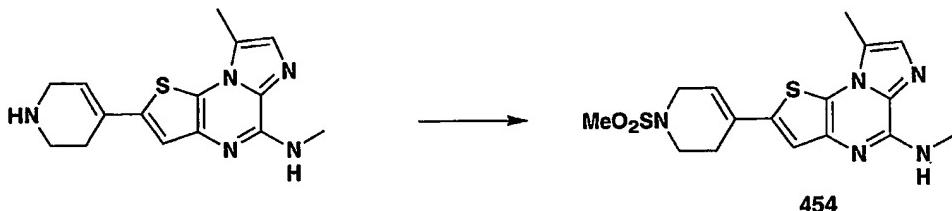


20 N-(2-(N-Tert-butyloxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-amine (0.028 g, 0.0701 mmol) was dissolved in a solution of trifluoroacetic acid (20%) in dichloromethane (3 mL). The reaction was stirred for 3 hours, then the solvent was evaporated to give the trifluoroacetic acid salt of Compound 453 (0.033 g, 89%). NMR (DMSO-d₆, 400 MHz) δ: 2.65 (3H, s),
25

2.74 (2H, br s), 2.97 (3H, s), 3.33 (2H, t, $J=6.1$ Hz), 3.74 (2H, br s), 6.19 (1H, br t),
7.29 (1H, s), 7.36 (1H, s).

Example 454

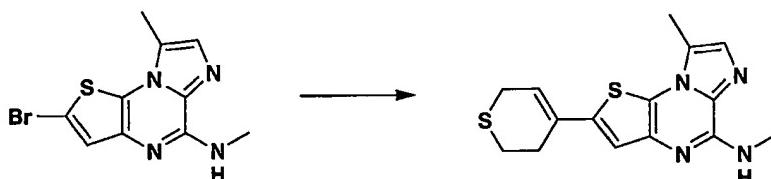
5



A solution of N-(2-(1,2,3,6-tetrahydropyridin-4-yl)-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-amine (0.011g, 0.0367 mmol) in dichloromethane (3 mL)
10 was treated with triethylamine (0.15 mL, 0.11 mmol) and methanesulfonyl chloride (4 μ L, 0.044 mmol) at 0°C. The reaction was stirred at room temperature for 3 hours, then quenched with water and diluted with dichloromethane. The organic layer was washed with water and brine then dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by Prep TLC to give Compound 454 (0.005 g, 36%). NMR (DMSO-d₆, 400 MHz) δ : 2.69 (5H, m), 2.96 (3H, s), 2.97 (3H, s), 3.41 (2H, d, $J=5.9$ Hz), 3.89 (2H, d, $J=3.1$ Hz), 6.23 (1H, t, $J=3.5$ Hz), 7.32 (1H, s), 7.35 (1H, s), 7.41 (1H, d, $J=5.1$ Hz). LRMS (ESI, m/z, M+H⁺) 378.

Example 455

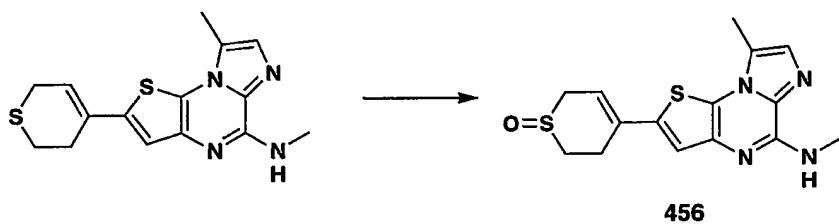
20



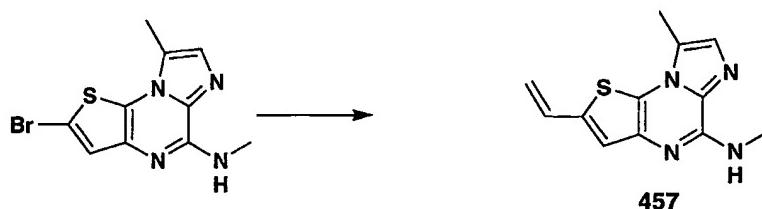
A stirred solution of N-(2-bromo-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-amine (0.100 g, 0.336 mmoles) in N-methylpyrrolidinone (10 mL) was treated with (3,6-dihydro-2H-thiopyran-4-yl)-trimethyl-stannane (0.196 g, 0.504 mmol), tris-

dibenzylideneacetone dipalladium (20 mgs) and triphenylarsine (30 mgs). The reaction was heated at 100°C overnight and was then diluted with ethyl acetate, washed with water (2x) and dried over anhydrous magnesium sulfate. After filtration, the organic phase was evaporated to give a residue which was purified by column chromatography (hexane / ethylacetate 50%) to give Compound 455 (0.014 g, 52%). NMR (DMSO-d₆, 400 MHz) δ: 2.67 (3H, s), 2.50-2.72 (2H, m), 2.86 (2H, t, J=5.8 Hz), 2.94 (3H, d, J=4.8 Hz), 3.30 (2H, m overlapped by HDO), 6.40 (1H, t, H = 5.8 Hz), 7.28-7.35. (3H, m).

10

Example 456

To a stirred solution of [2-(3,6-dihydro-2H-thiopyran-4-yl)-8-methyl-1-thia-4,5,8a-triaza-as-indacen-5-yl]-methyl-amine (0.009 g, 0.0284 mmol) in dichloromethane (3 mL) at -78°C was added peracetic acid (0.1N in acetic acid, 0.3 mL). The reaction was slowly warmed up to room temperature over a period of 5 hours. The reaction was then quenched with dimethylsulfide (1N in methanol, 10 eq), diluted with dichloromethane, washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by Prep HPLC (ammonium acetate/water/acetonitrile) to give Compound 456 (0.007 g, 78%) as a solid. NMR (DMSO-d₆, 400 MHz) δ: 2.51-2.56 (1H, m overlapped by DMSO-d₆), 2.68-2.69 (1H, m), 2.69 (3H, s), 2.81-3.18 (2H, m), 2.97 (3H, d, J=4.6 Hz), 3.44 (1H, dd, J=16.6 and 5.0 Hz), 3.67 (1H, dd, J=16.6 and 5.0 Hz), 6.11 (1H, t, J=5.0 Hz), 7.35 (1H, s), 7.40 (1H, s), 7.42 (1H, q, J=4.6 Hz). LRMS (ESI, m/z, M+H⁺) 333.

Example 457

5

A stirred solution of N-(2-bromo-8-methyl-1-thia-4,6,8a-triaza-as-indacen-5-yl)-N-methyl-amine (0.120 g, 0.403 mmoles) in N-methylpyrrolidinone (8 mL) was treated with a solution of vinyltributylstannane (0.170 g, 0.53 mmol) in N-methylpyrrolidinone (1 mL) and tetrakistriphenylphosphinepalladium(0) (20 mgs).
 10 The reaction was heated at 115°C for 4 hours. The reaction was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (50 to 100% ethyl acetate/hexane) and by Prep HPLC (acetonitrile / water / trifluoroacetic acid) to give Compound 457 as a trifluoroacetic acid salt (0.080 g, 81%). NMR (DMSO-d₆, 400 MHz) δ: 2.68 (3H, s), 2.96 (3H, s), 5.23 (1H, d, J=11.0), 5.62 (1H, d, J=17.4 Hz), 6.94 (1H, dd, J=17.4 and 11.0 Hz), 7.29 (1H, s), 7.34 (1H, s), 7.50 (1H, m). IR (ν, cm⁻¹): 3298, 1684, 1594, 1575. LRMS (ESI, m/z, M+H⁺) 245. HRMS for C₁₂H₁₂N₄S calcd: 244.0783; found: 244.0777.

20

The following conditions apply to Examples 458-510

Thin-layer chromatography was done on E. Merck silica gel 60 F₂₅₄ plates (0.5 mm). Hplc purity determinations were done using either a Shimadzu LC-10AS with a SPD-10AV UV-Vis detector and one of the following columns; YMC Combiscreen 25 ODS-A (4.6 x 50 mm), or HP Zorbax SB-C18 (4.6 x 750 mm); or, an HP 1090 DR5 with a diode array detector and a Waters Nova-Pak C18 column (3.9 x 150 mm). Infrared spectra were recorded on a Nicolet Protégé 460 FTIR as thin films or KBr pellets. ¹HNMR spectra were recorded on either a Bruker AMX-400 or a Bruker ARX-500 NMR spectrometer.

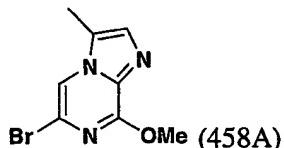
Example 458



5

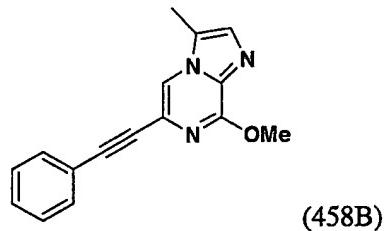
458

Step A:



To a mixture of methanol (2 mL) and MeONa in methanol (25% wt, 88 μ L 10 0.397 mmol) was added the compound of Example 1D (0.1g, 0.406 mmol). The reaction mixture was heated under reflux for 3 h and the solvent was evaporated to dryness. Water was added to the residue and the target compound was extracted with ethyl acetate (3 x 25 mL). The organic solution was dried ($MgSO_4$) and concentrated 15 in vacuo to give compound 458A as a beige solid. (91 mg, 93%); mp 127-130 °C; IR (KBr , cm^{-1}) 3062, 2996, 2947, 1743, 1521, 1109; 1H NMR (DMSO) δ 8.41 (s, 1H), 7.53 (s, 1H), 4.10 (s, 3H), 2.56 (s, 3H); LC/MS 100% (220 nm), m/z ($M + H^+$) 242.

20 Step B:

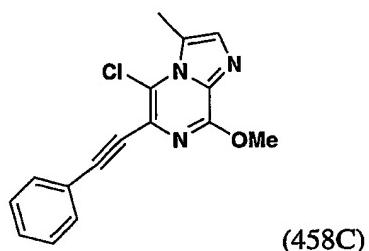


To a solution of Compound 458A (2.0 g, 8.26 mmol) in DMF (10 mL) in a sealed tube was added tetrakis(triphenylphosphine)palladium(0) (477 mg, 0.413 mmol) copper iodide (126 mg, 0.661 mmol) phenylacetylene (1.36 mL, 12.4 mmol) and triethylamine (4.60 mL, 33 mmol). The reaction mixture was heated at 70 °C for

2.5 h. Then the solvent was evaporated in vacuo and the crude material was purified on silicagel dried column using AcOEt : Hexane (2:1) to (4:1) to afford compound 458B as a beige solid. (2.10 g, 96%); mp 112 °C; IR (KBr, cm⁻¹) 3420, 1700, 1652, 1499, 1209; ¹H NMR (DMSO) δ 8.43 (s, 1H), 7.60-7.58 (m, 2H), 5 7.47-7.44 (m, 2H), 4.05 (s, 3H), 3.29 (s, 3H). LC/MS 100% (220 nm), m/z (M + H⁺) 264.

Step C :

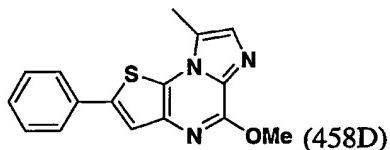
10



To compound 458B (8.4 g 31.9 mmol) in THF was added N-chlorosuccinimide (4.69 g, 35.01 mmol). The reaction mixture was stirred at 55 °C for 15 18 h. Then, the solvent was evaporated in vacuo and the crude material was purified on silicagel dry column using AcOEt : Hexane (2:1) to (4:1) as solvents to afford compound 458C as a yellow solid (1.71 g, 18%); mp 105 °C; IR (KBr, cm⁻¹) 3446, 1700, 1532, 1219; ¹H NMR (DMSO) δ 7.62-7.60 (m, 2H), 7.50-7.46 (m, 4H), 4.04 (s, 3H), 2.77(s, 3H); LC/MS 95.1% (220 nm), m/z (M + H⁺) 298.

20

Step D :

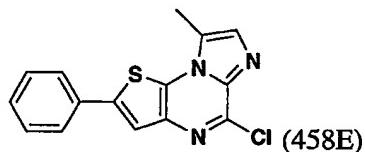


To compound 458C (200 mg, 0.672 mmol) in DMF was added sodium sulfide nonahydrate (403 mg, 1.68 mmol). The reaction mixture was stirred in a sealed tube at 90 °C for 18 h. Then, DMF was evaporated in vacuo and the crude material was purified on silicagel dry column using AcOEt : Hexane (1:2) to (2:1) as solvents to

afford compound 458D as a beige solid (0.160 mg, 81%); mp 127-130 °C; IR (KBr, cm⁻¹) 3159, 3082, 1695, 1192; ¹H NMR (DMSO) δ 7.91 (s, 1H), 7.82-7.79 (m, 2H), 7.51-7.46 (m, 3H), 7.41-7.37 (m, 1H), 4.10 (s, 3H), 2.79 (s, 3H); LC/MS 96% (220 nm), m/z (M + H⁺) 296.

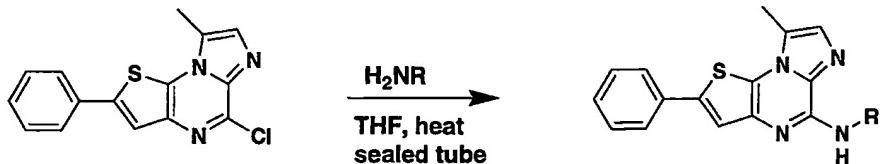
5

Step E :



A solution of compound 458D (300 mg, 1.07 mmol) in phosphorus oxychloride (12 mL) was heated in a sealed tube at 90 °C for 18 h. Then, phosphorus oxychloride was evaporated in vacuo and ice (50mL) was added to the solid. The aqueous solution was neutralized with a saturated solution of sodium bicarbonate (pH = 8) and the organic material was extracted with AcOEt : THF (4:1) (4X25 mL). Combined organic solutions were dried (MgSO₄) and concentrated in vacuo to afford compound 458E as a white solid. (279 mg, 87%); mp 197 °C, IR (KBr, cm⁻¹) 3421, 3077, 1408, 1313; ¹H NMR (DMSO) δ 7.81 (s, 1H), 7.62-7.60 (m, 2H), 7.50 (s, 1H), 7.32-7.24 (m, 2H), 7.19-7.16 (m, 1H), 2.62 (s, 3H); LC/MS 100% (220 nm), m/z (M + H⁺) 300.

20 Step F (Method 1) :

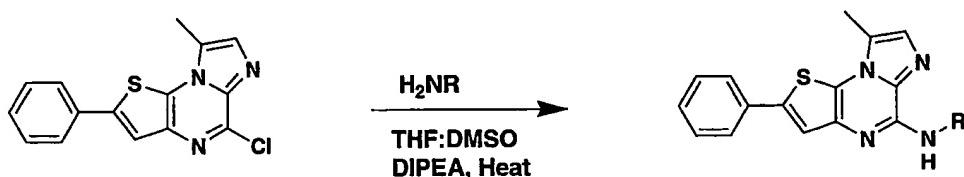


To a solution of compound 458E (55 mg, 0.183 mmol) in THF (3 mL) was added the amine (1.83 mmol) and the reaction mixture was stirred in a sealed tube at 85 °C until completion (1 to 10 days). Then, THF was evaporated in vacuo and crude material was purified by silicagel dry column using CH₂Cl₂ : MeOH as solvents, by

crystallization in hot isopropanol or by preparative HPLC to afford the desired product.

Step F (Method 2) :

5



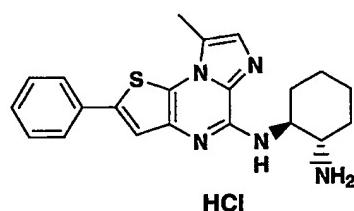
To a solution of compound 458E (55 mg, 0.183 mmol) in THF : DMSO (2 mL:2 mL) was added the amine (1.83 mmol) and N,N-diisopropylethylamine (368 μ L, 4.03 mmol). The reaction mixture was stirred in a sealed tube at 120 °C until completion (2 to 8 days). Then, solvents were evaporated in vacuo and crude material was purified by silicagel dry column using CH₂Cl₂ : MeOH as solvents, by crystallization in hot isopropanol or by preparative HPLC to afford the desired product.

15 Step G (Compound 458):

Compound 458 was prepared from compound 458E and 1-(2-aminoethyl)piperidine using Step F (method 1), and was retrieved as an off-white solid. (61%); mp 137-139 °C; IR (KBr, cm⁻¹) 3326, 2929, 1559, 1404; ¹H NMR (DMSO) 7.78-7.75 (m, 3H), 7.48-7.44 (m, 2H), 7.38-7.36 (m, 2H), 7.12 (br s, 1H), 3.62-3.57 (m, 2H), 2.74 (s, 3H), 2.58 (br s, 2H), 2.42 (br s, 4H), 1.54-1.51 (m, 4H), 1.42-1.40 (m, 2H); MS (⁺ESI, M + H⁺) m/z 392; HPLC: 96.13% (220 nm); HRMS calcd for C₂₂H₂₅N₅S: 392.1908; found 392.1907

Example 459

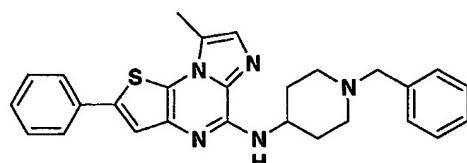
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459

Compound 459 was prepared from intermediate 458E and trans-1,2-diaminocyclohexane using Step F (method 1), described in the synthesis of Example 458. Compound 459 was retrieved as a yellow solid. (12%); mp 162-164 °C; IR (KBr, cm⁻¹) 3360, 2920, 2858; ¹H NMR (DMSO) 7.72-7.71 (d, J=7.4, 2H), 7.64 (s, 1H), 7.45-7.43 (m, 2H), 7.38-7.33 (m, 2H), 4.07-4.01 (m, 1H), 3.06-2.99 (m, 1H), 2.71 (s, 3H), 2.43 (br s, 2H), 2.01-1.15 (br m, 6H); MS (¹ESI, M + H⁺) m/z 378; HPLC: 99.0% (220 nm); HRMS calcd for C₂₁H₂₃N₅S: 377.1674; found 377.1693

10

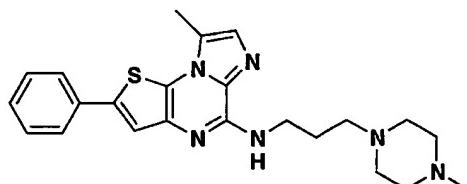
Example 460

460

15

Compound 460 was prepared from intermediate 458E and 4-amino-1-benzylpiperidine using Step F (method 1), described in the synthesis of Example 458. Compound 460 was retrieved as a beige solid. (10%); mp 91-94 °C; IR (KBr, cm⁻¹) 3415, 2922, 2799, 1540, 1074; ¹H NMR (DMSO) 7.78-7.76 (m, 3H), 7.47-7.43 (m, 2H), 7.37-7.26 (m, 7H), 7.12-7.10 (d, J=8.2, 2H), 4.12-4.07 (m, 1H), 3.5 (br s, 2H), 2.85 (br d, 2H), 2.73 (s, 3H), 2.10 (br t, 2H), 1.91 (br d, 2H), 1.72 (m, 2H); MS (¹ESI, M + H⁺) m/z 454; HPLC: 99.0% (220 nm); HRMS calcd for C₂₇H₂₇N₅S: 454.2065; found 454.2074

25

Example 461

461

Compound 461 was prepared from intermediate 458E and 1-(3-aminopropyl)-4-methylpiperidine using Step F (method 1), described in the synthesis of Example 458. The compound was retrieved as a beige solid. (11%); mp 129-131 °C; IR (KBr, cm⁻¹) 3424, 2933, 2833, 2788, 1550, 1166; ¹H NMR (DMSO) 7.77 (d, J=7.5, 2H), 7.74 (s, 1H), 7.61 (t, J=5.5, 1H), 7.48-7.44 (m, 2H), 7.37-7.34 (m, 2H), 3.53 (m, 2H), 2.74 (s, 3H), 2.51-2.28 (m, 10H), 2.17 (s, 3H), 1.85-1.77 (m, 2H); MS (^{+ESI}, M + H⁺) m/z 421; HPLC: 92.5% (220 nm); HRMS calcd for C₂₃H₂₈N₆S: 421.2174; found 421.2164

10

Example 462

462

15 Compound 462 was prepared from intermediate 458E and N,N-dimethylethylenediamine using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a beige solid. (18 %); mp 133-135 °C; IR (KBr, cm⁻¹) 3743, 3266, 2939, 2812, 2770, 1559, 1038; ¹H NMR (DMSO) 7.77-7.74(m, 3H), 7.47-7.43 (m, 2H), 7.08 (br t, 1H), 3.57. (m, 2H), 2.73 (s, 3H), 2.57-2.53 (m, 2H), 2.23 (s, 6H), 1.85-1.77 (m, 2H); MS (^{+ESI}, M + H⁺) m/z 351; HPLC: 98.7% (220 nm); HRMS calcd for C₁₉H₂₁N₅S: 351.1518; found 351.1518

25

Example 463

463

Compound 463 was prepared from intermediate 458E and ethanolamine using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a beige solid. (58 %); mp 104-106 °C; IR (KBr, cm⁻¹) 3370, 3148, 2911, 2848, 1554, 1071; ¹H NMR (DMSO) 7.78-7.74 (m, 3H), 7.51-7.44 (m, 2H), 5 7.41-7.34 (m, 2H), 7.21 (br t, 1H), 4.83 (t, J=5.3 1H), 3.67-3.56 (m, 4H), 2.74 (s, 3H); m/z 324; HPLC: 94.8% (220 nm); HRMS calcd for C₁₇H₁₆N₄OS: .324.1045; found 324.1038

Example 464

10



464

Compound 464 was prepared from intermediate 458E and glycaminamide hydrochloride using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a beige solid. (36 %); mp 268 °C; IR (KBr, cm⁻¹) 3375, 3277, 1652, 1558, 1541, 1331; ¹H NMR (DMSO) 7.78-7.76 (m, 3H), 7.47-7.33 (m, 6H), 7.13 (br s, 1H), 4.03 (d, J=5.7 1H), 2.74 (s, 3H); m/z 338; HPLC: 99.0% (220 nm); HRMS calcd for C₁₇H₁₅N₅OS: 337.0998; found 337.1006

20

Example 465



465

25

Compound 465 was prepared from intermediate 458E and histamine dihydrochloride using Step F (method 2), described in the synthesis of Example 458.

The desired compound was retrieved as an off-white solid; (12%); mp 205 °C; IR (KBr, cm⁻¹) 3278, 3095, 1567, 1422; ¹H NMR (DMSO) 7.78-7.77 (m, 3H), 7.58-7.44 (m, 4H), 7.37-7.34 (m, 2H), 6.94 (br s, 1H), 3.75 (td, J=6.4, 7.1, 2H), 2.74 (s, 3H), 2.93-2.87 (br s, 2H), 2.74 (s, 3H); MS (⁺ESI, M + H⁺) m/z 375 ; HPLC: 100 % (220 nm); HRMS calcd for C₂₀H₁₈N₆S: 374.1314; found 374.1305

Example 466



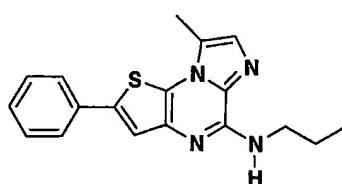
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466

Compound 466 was prepared from intermediate 458E and 4-(2-aminoethyl)morpholine using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as an off-white solid (35 %); mp 153 °C; IR (KBr, cm⁻¹) 3326, 2929, 1559, 1404; ¹H NMR (DMSO) 7.78-7.75 (m, 3H), 7.48-7.44 (m, 2H), 7.38-7.36 (m, 2H), 7.12 (br s, 1H), 3.62-3.57 (m, 2H), 2.74 (s, 3H), 2.58 (br s, 2H), 2.42 (br s, 4H), 1.54-1.51 (m, 4H), 1.42-1.40 (m, 2H); MS (⁺ESI, M + H⁺) m/z 392; HPLC: 96.13% (220 nm); HRMS calcd for C₂₂H₂₅N₅S: 392.1908; found 392.1907

20

Example 467



25

467

Compound 467 was prepared from intermediate 458E and propylamine using Step F (method 1), described in the synthesis of Example 458. The desired compound

was retrieved as an off-white solid (48 %); mp 166 °C; IR (KBr, cm⁻¹) 3359, 2963, 2923, 1558, 1421; ¹H NMR (DMSO) 7.78-7.75 (m, 3H), 7.48-7.44 (m, 2H), 7.41-7.33 (m, 3H), 3.46 (br quad, 2H), 2.74 (s, 3H), 1.67 (m, 2H), 0.94 (br t, 3H); MS (^{+ESI}, M + H⁺) m/z 323; HPLC: 97.5% (220 nm); HRMS calcd for C₁₈H₁₈N₄S: 322.1252; found 322.1259

Example 468



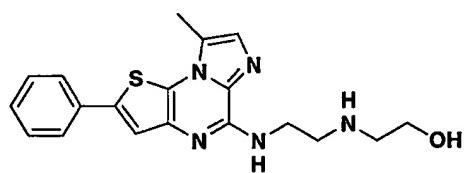
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468

Compound 468 was prepared from intermediate 458E and 3-amino-1,2-propanediol using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a light yellow solid (34 %); mp 187 °C; IR (KBr, cm⁻¹) 3403, 3253, 2921, 1540, 1399; ¹H NMR (DMSO) 7.78-7.77 (m, 2H), 7.74 (s, 1H), 7.48-7.44 (m, 2H), 7.39-7.36 (m, 2H), 7.10 (br t, 1H), 5.02 (d, J=5.1, 1H), 4.70 (br t, 1H), 3.85-3.65 (m, 2H), 3.45-3.40 (m, 4H), 2.74 (s, 3H); MS (^{+ESI}, M + H⁺) m/z 355; HPLC: 97.7% (220 nm); HRMS calcd for C₁₈H₁₈O₂N₄S: 354.1150; found 354.1129

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Example 469



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469

Compound 469 was prepared from intermediate 458E and 2-(2-aminoethyl)ethanol using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a light yellow solid (30 %);

mp >220 °C; IR (KBr, cm⁻¹) 3420, 3324, 2920, 2732, 1558, 1361; ¹H NMR (DMSO) 7.78-7.74 (m, 4H), 7.48-7.44 (m, 3H), 7.40-7.36 (t, J=7.3, 1H), 5.3 (br s, 1H), 3.80 (br q, 2H), 3.68 (br t, 2H), 3.50 (m, 2H), 3.39 (br t, 2H), 2.76 (s, 3H); MS (^{+ESI}, M + H⁺) m/z 368; HPLC: 94.7% (220 nm); HRMS calcd for C₁₉H₂₁ON₅S: 367.1467; found 5 367.1475

Example 470



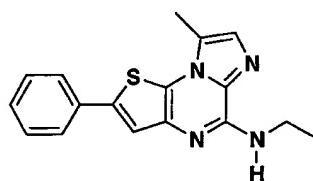
10

470

Compound 470 was prepared from intermediate 458E and 1-(2-aminoethyl)pyrrolidine using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a light yellow solid (13 %); mp 15 115 °C; IR (KBr, cm⁻¹) 3395, 2959, 2788, 1558, 1540; ¹H NMR (DMSO) 7.79-7.76 (m, 3H), 7.48-7.44 (m, 2H), 7.38-7.34 (m, 2H), 7.18 (br t, 1H), 3.62 (br q, 2H), 2.74 (br s, 5H), 2.56-2.44 (br m, 3H), 1.72-1.66 (br m, 5H), 2.76 (s, 3H); MS (^{+ESI}, M + H⁺) m/z 378; HPLC: 97.1% (220 nm); HRMS calcd for C₂₁H₂₃N₅S: 377.1674; found 377.1665

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Example 471



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471

Compound 471 was prepared from intermediate 458E and ethylamine using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a white solid (48 %); mp 205 °C; IR (KBr, cm⁻¹) 3352, 2964, 2927,

1554, 1422; ^1H NMR (DMSO) 7.78-7.76 (m, 3H), 7.48-7.44 (m, 2H), 7.42-7.34 (m, 3H), 3.53 (q d, $J=5.6, 7.1$ 2H), 2.74 (s, 3H), 1.23 (t, $J=7.06$ 3H); MS ($^{\ddagger}\text{ESI}$, M + H $^{+}$) m/z 309; HPLC: 99.2% (220 nm); HRMS calcd for C₁₇H₁₆N₄S: 308.1096; found 308.1088

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Example 472



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472

Compound 472 was prepared from intermediate 458E and 1-(2-aminoethyl)thiomorpholine using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a light yellow solid (64 %); mp 169-72 °C; IR (KBr, cm⁻¹) 3399, 2911, 2809, 1541, 1398; ^1H NMR (DMSO) 7.78-7.75 (m, 3H), 7.48-7.44 (m, 2H), 7.38-7.34 (m, 2H), 7.18 (t, $J=5.6, 1\text{H}$) 3.60 (br q, 2H), 2.77-2.74 (m, 7H), 2.67-2.61 (m, 6H); MS ($^{\ddagger}\text{ESI}$, M + H $^{+}$) m/z 410; HPLC: 93.0 % (220 nm); HRMS calcd for C₁₇H₁₆N₄S: 410.1473; found 410.1466

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Example 473



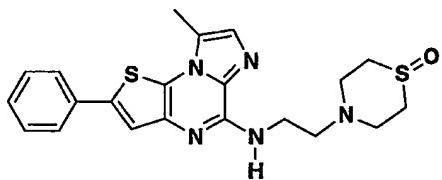
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473

To the compound of example 472 (26 mg, 0.0634 mmol) in CH₂Cl₂ (2 mL) at -15 °C was added dropwise a peracetic acid solution in acetic acid (0.1M, 1.90 mL, 0.190 mmol). After 10 min. the reaction mixture was warmed up to 0 °C and stirred 30 min. Then, a solution of dimethylsulfure in CH₂Cl₂ (1M, 0.064 mmol) was added and solvents were evaporated in vacuo. The crude material in DMF (2 mL) was treated

with a basic resin (MP-Carbonate, 2.0 g) for two h. The resin was removed by filtration and DMF evaporated in vacuo. The crude material was crystallized in hot isopropanol to afford the desired product as a light beige solid (20 %); mp 203-205 °C; IR (KBr, cm⁻¹) 3420, 2931, 1566, 1539, 1007; ¹H NMR (MeOD) 7.70 (d, J=7.2, 5 2H), 7.56 (s, 1H), 7.43 (dd, J=7.7, 7.2, 2H), 7.33 (m, 2H), 4.21-4.15 (m, 3H), 3.79 (t, 6.5, 2H), 3.63-3.55(m, 2H), 3.25(m, 2H), 3.03 (m, 2H), 2.76 (s, 3H); MS (⁷ESI, M + H⁺) m/z 442; HPLC: 95.2 % (220 nm); HRMS calcd for C₂₁H₂₃N₅O₂S₂: 442.1371; found 442.1378.

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Example 474

474

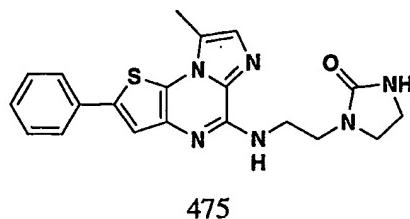
15

To the compound of example 472 (26 mg, 0.0634 mmol) in CH₂Cl₂ (2 mL) at -15 °C was added dropwise a peracetic acid solution in acetic acid (0.1M, 0.64 mL, 0.064 mmol). After 10 min. the reaction mixture was warmed up to 0 °C and stirred 30 min. Then, a solution of dimethylsulfide in CH₂Cl₂(1M, 0.064 mmol) was added and solvents were evaporated in vacuo. The crude material in DMF (2 mL) was treated with a basic resin (MP-Carbonate, 2.0 g) for two h. The resin was removed by filtration and DMF evaporated in vacuo. The crude material was crystallized from hot isopropanol to afford the desired product as a light beige solid. (46 %); mp 171-174 °C; IR (KBr, cm⁻¹) 3421, 2921, 1558, 1540, 1029; ¹H NMR (DMSO) 7.79-7.75 (m, 3H), 7.47-7.44 (m, 2H), 7.38-7.34 (m, 2H), 7.24 (t, J=6.0, 1H), 3.63 (td, J=6.4, 6.0, 2H), 3.01-2.86 (m, 4H), 2.79-2.68 (m, 9H); MS (⁷ESI, M + H⁺) m/z 426; HPLC: 94.7 % (220 nm); HRMS calcd for C₂₁H₂₃N₅OS₂: 426.1422; found 426.1426.

30

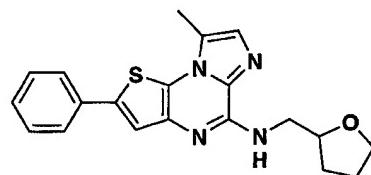
Example 475

240



Compound 475 was prepared from intermediate 458E and 1-(2-aminoethyl)imidazolidin-2-one using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a light-yellow solid (39 %); mp 193-195 °C; IR (KBr, cm⁻¹) 3271, 1684, 1559, 1275; ¹H NMR (DMSO) 7.79-7.76 (m, 3H), 7.48-7.42 (m, 3H), 7.37-7.34 (m, 2H), 6.25 (s, 1H), 3.60 (br q, 2H), 3.49-3.45 (br t, 2H), 3.38-3.34 (m, 2H), 3.28-3.19 (m, 2H), 2.74 (s, 3H); MS (¹ESI, M + H⁺) m/z 493; HPLC: 95.0 % (220 nm); HRMS calcd for C₂₀H₂₀N₆OS: 392.1419; found 392.1434

Example 476



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476

Compound 476 was prepared from intermediate 458E and tetrahydrofurfurylamine using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a light-yellow solid (56 %); mp 169 °C; IR (KBr, cm⁻¹) 3264, 2965, 1556, 1078; ¹H NMR (DMSO) 7.79-7.77 (m, 3H), 7.48-7.44 (m, 2H), 7.39-7.34 (m, 2H), 7.17 (t, J=6.2, 1H), 4.17(m, 1H), 3.82 (br q, 1H), 3.69-3.52(m, 3H), 2.74 (s, 3H), 1.96-1.66 (m, 4H); MS (¹ESI, M + H⁺) m/z 365; HPLC: 93.1 % (220 nm); HRMS calcd for C₂₀H₂₀N₄OS: 364.1358; found 364.1358

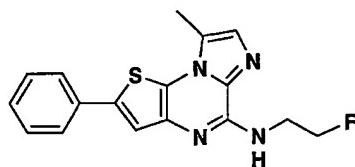
Example 477



477

Compound 477 was prepared from intermediate 458E and 2-methoxyethylamine using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a light-yellow solid (49 %); mp 185 °C; IR (KBr, cm⁻¹) 3264, 2923, 1559, 1119; ¹H NMR (DMSO) 7.78-7.77 (m, 3H), 7.48-7.44 (m, 2H), 7.38-7.34 (m, 2H), 7.17 (t, J=5.6, 1H) 3.68 (br q, 2H), 3.59 (br t, 2H), 3.31(s, 3H), 2.74 (s, 3H); MS ([†]ESI, M + H⁺) m/z 339; HPLC: 94.9 % (220 nm); HRMS calcd for C₁₈H₁₈N₄OS: 338.1201; found 338.1208

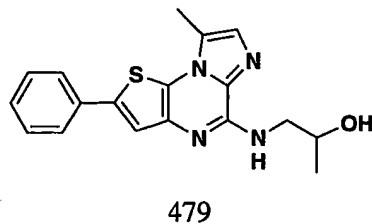
Example 478



478

Compound 478 was prepared from intermediate 458E and 2-fluoroethylamine using Step F (method 2), described in the synthesis of Example 458. The desired compound was retrieved as a beige solid (22 %); mp 189 °C; IR (KBr, cm⁻¹) 3384, 2923, 1547, 1404, 1034; ¹H NMR (DMSO) 7.79-7.77 (m, 3H), 7.56 (t, J=5.8, 1H), 7.48-7.44 (m, 2H), 7.41-7.36 (m, 2H), 4.66 (dt, J=47.6, 5.6, 2H), 3.82(d q, J=24.2, 5.4, 2H), 2.74 (s, 3H); MS (^{+ESI}, M + H⁺) m/z 327; HPLC: 95.4 % (220 nm); HRMS calcd for C₁₇H₁₅FN₄S: 327.1079; found 327.1082

Example 479



Compound 479 was prepared from intermediate 458E and DL-1-amino-2-propanol using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a beige solid (59 %); mp 225 °C; IR (KBr, cm⁻¹) 3377, 2961, 2916, 1540, 1420, 1144; ¹H NMR (DMSO) 7.78-7.77 (d, J=7.14, 2H), 7.74 (s, 1H), 7.48-7.45 (m, 2H), 7.39-7.34 (m, 2H), 7.11 (t, J=5.6, 1H), 4.92 (d, J=3.55 1H), 3.53 (m, 1H), 3.40 (m, 1H), 3.37 (m, 1H), 2.75 (s, 3H); MS (¹ESI, M + H⁺) m/z 339; HPLC: 97.5 % (220 nm); HRMS calcd for C₁₈H₁₈N₄OS: 339.1279; found 339.1286

Example 480

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480

Compound 480 was prepared from intermediate 458E and 2(1H-pyrrol-1-yl)-1-ethanamine using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a light brown solid (48 %); IR (KBr, cm⁻¹) 3314, 2941, 1558, 1540, 1088; ¹H NMR (DMSO) 7.79-7.77 (m, 3H), 7.48-7.45 (m, 3H), 7.38-7.34 (m, 2H), 6.80 (d, J=2.2, 2H), 5.99(d, J=2.2 2H), 4.22 (t, J=6.3, 2H), 3.82 (td, J=6.1, 5.9, 2H), 2.75 (s, 3H); MS (¹ESI, M + H⁺) m/z 374; HPLC: 95.5 % (220 nm); HRMS calcd for C₂₁H₁₉N₅S: 374.1437; found 374.1439

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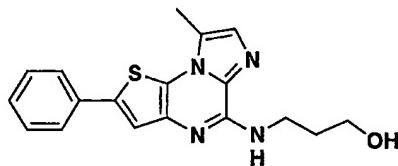
Example 481



481

Compound 481 was prepared from intermediate 458E and DL-2-amino-1-propanol using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a beige solid (38 %); mp 175 °C; IR (KBr, cm⁻¹) 3395, 2973, 1546, 1424, 1095; ¹H NMR (DMSO) 7.78-7.76 (m, 3H), 7.48-7.45 (m, 2H), 7.38-7.34 (m, 2H), 6.87 (d, J=7.9, 1H), 4.85 (t, J=5.5 1H), 4.31(m, 1H), 3.57 (m, 1H), 3.52 (m, 1H), 2.74 (s, 3H); LC/MS 90 % (220 nm), m/z (M + H⁺) 339

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Example 482

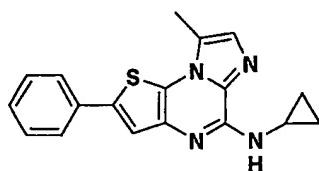
482

15

Compound 482 was prepared from intermediate 458E and 3-amino-1-propanol using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a beige solid (46 %); IR (KBr, cm⁻¹) 3304, 2935, 2909, 20 1589, 1570, 1421; ¹H NMR (DMSO) 7.78-7.76 (d, J=7.0, 2H), 7.75 (s, 1H), 7.48-7.44 (m, 2H), 7.42-7.33 (m, 3H), 4.60(t, J=5.3, 1H), 3.59-3.51 (m, 4H), 2.74 (s, 3H), 1.84-1.78 (m, 2H); MS (⁺ESI, M + H⁺) m/z 339; HPLC: 95.7 % (220 nm); HRMS calcd for C₁₈H₁₈N₄OS: 339.1280; found 339.1278

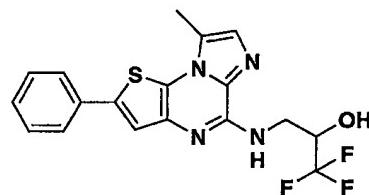
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Example 483



Compound 483 was prepared from intermediate 458E and cyclopropylamine
 5 using Step F (method 1), described in the synthesis of Example 458. The desired compound was retrieved as a beige solid (50 %); IR (KBr, cm⁻¹) 3292, 3003, 1539, 1422; ¹H NMR (DMSO) 7.73 (s, 1H), 7.70 (d, J=6.9, 2H), 7.46 (d, J=3.3, 1H), 7.40-7.36 (m, 2H), 7.29-7.25 (m, 2H), 2.90-2.86 (m, 1H), 2.66 (s, 3H), 0.70-0.58 (m, 4H); MS (^{+ESI}, M + H⁺) m/z 321; HPLC: 98.0 % (220 nm); HRMS calcd for C₁₈H₁₆N₄S: 10 321.1174; found 321.1177

Example 484

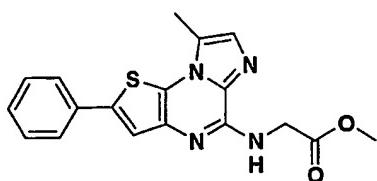


15

Compound 484 was prepared from intermediate 458E and 3-amino-1,1,1-trifluoro-2-propanol using Step F (method 1), described in the synthesis of Example 20 458. The desired compound was retrieved as a beige solid (33 %); IR (KBr, cm⁻¹) 3391, 3078, 2851, 1541, 1423, 1166, 1130; ¹H NMR (DMSO) 7.78 (d, J=7.0, 1H), 7.77 (s, 1H), 7.48-7.34 (m, 5H), 6.52 (d, J=5.8, 1H), 4.49-4.42(m, 1H), 3.88-3.83 (m, 1H), 3.66-3.60(m, 1H), 2.75 (s, 1H); LC/MS 98.2 % (220 nm), m/z (M + H⁺) 393

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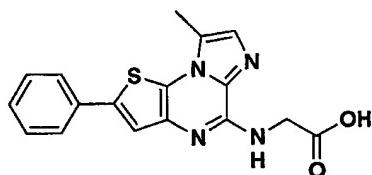
Example 485



Compound 485 was prepared from intermediate 458E and glycine methy ester hydrochloride using Step F (method 2), described in the synthesis of Example 458.

5 The desired compound was retrieved as a light yellow solid (24 %); IR (KBr, cm⁻¹) 3421, 3268, 2923, 1747, 1559, 1540, 1208; ¹H NMR (DMSO) 7.79-7.76 (m, 4H), 7.48-7.43 (m, 3H), 7.38 (br t, 1H), 4.25 (d, J=6.1, 2H), 3.64 (s, 3H), 2.76 (s, 3H); MS (¹ESI, M + H⁺) m/z 353; HPLC: 90.5 % (220 nm); HRMS calcd for C₁₈H₁₆N₄O₂S: 10 353.1082; found 353.1072

Example 486

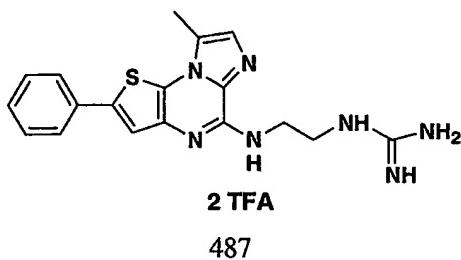


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486

Compound 486 was prepared from the compound of Example 485 (12 mg, 0.034 mmol), which was treated with a solution of KOH (19 mg, 0.34 mmol) in MeOH : H₂O (0.5 mL:0.5 mL) for 2 h at 23 C. Then, the reaction mixture was purified by preparative HPLC using C18 column to afford the desired product as a beige solid (45 %); IR (KBr, cm⁻¹) 3407, 1558, 1437; ¹H NMR (DMSO) 7.78-7.76 (m, 3H), 7.47-7.43 (m, 2H), 7.39-7.33 (m, 2H), 3.91-3.89 (br d, 2H), 2.75 (s, 3H); LC/MS 93.3 % (220 nm), m/z (M + H⁺) 339

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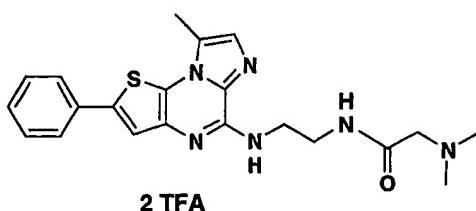
Example 487



To a solution of the compound of Example 9 (55 mg, 0.170 mmol) in THF : H₂O (15 mL:1 mL) at 23 °C was added 1,3-Bis(t-butoxycarbonyl)-2-methyl-2-thiopseudourea (54 mg, 0.187 mmol). The reaction mixture was stirred at 23 °C for 96 h and at 60 °C for 4 h. Then, H₂O was added and the organic material was extracted with AcOEt : THF (4:1) (3x 15 mL). The combined organic solutions was dried (MgSO₄) concentrated and purified preparative HPLC using C18 column.

Elution solvents were evaporated and the organic solid was dissolved in CH₂Cl₂ (2 mL). The solution was cooled to 0 °C and TFA (1 mL) was added. The reaction mixture was stirred at 23 °C for 18 h and solvents were evaporated in vacuo to afford the TFA salt of the desired product as a light yellow solid (51 %); IR (KBr, cm⁻¹) 3377, 1677, 1437, 1203, 1135; ¹H NMR (DMSO) 7.77 (d, J=7.1, 2H), 7.74 (s, 1H), 7.69 (br t, 1H), 7.56 (br t, 1H), 7.49 (br t, 2H), 7.43 (s, 1H), 7.38 (m, 1H), 3.64 (td, J=6.0, 6.2, 2H), 3.42 (td, J=6.0, 6.1, 2H), 2.76 (s, 3H); MS (¹ESI, M + H⁺) m/z 366; HPLC: 94.7 % (220 nm); HRMS calcd for C₁₈H₁₉N₇S: 365.1423; found 365.1455.

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Example 488

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488

To a solution of N,N-dimethylamine glycine hydrochloride in DMF was added 1,3-diisopropylcarbodiimide (73 μ L, 0.464 mmol), hydroxybenzotriazole (63 mg, 0.464 mmol), 4-dimethylaminopyridine (4 mg, 0.0309 mmol), N,N-diisopropylethylamine (28 μ L, 0.309 mmol) and the compound of Example 9 (100 mg, 0.309 mmol). The reaction mixture was stirred at 23 $^{\circ}$ C for 18 h. The reaction mixture was poured into a SPE-SCX column and was eluted with a solution of ammonia in methanol (2N, 40 mL). Solvent was evaporated in vacuo and crude material was purified on preparative HPLC with a C18 column using acidic conditions to afford the TFA salt of the desired product as a light yellow glassy compound (15 %); IR (KBr, cm $^{-1}$) 3431, 1653, 1559, 1203, 1129; 1 H NMR (DMSO + D₂O) 8.62 (t, J=5.5, 1H), 7.75 (d, J=7.5, 2H), 7.68 (s, 1H), 7.47 (dd, J=7.7, 7.6, 2H), 7.40-7.35 (m, 2H), 3.84 (s, 2H), 3.60 (m, 2H), 3.48-3.46 (m, 2H), 2.77 (s, 6H), 2.73 (s, 3H); MS ($^{+}$ ESI, M + H $^{+}$) m/z 409; HPLC: 96 % (220 nm); HRMS calcd for C₂₁H₂₄N₆OS: 409.1811; found 409.1804.

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Example 489

489

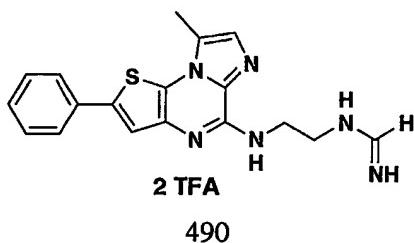
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To a solution of the compound of Example 9 (60 mg, 0.186 mmol) in THF (3 mL) at 23 $^{\circ}$ C was added triethylamine (78 μ L, 0.223 mmol) and acetylchloride (16 μ L, 23 mmol). The reaction mixture was stirred at 23 $^{\circ}$ C for 18 h. Then, solvent was evaporated in vacuo and a sodium bicarbonate saturated solution was added (10 mL). Organic material was extracted with AcOEt : THF (4:1) (3x 10 mL). Organic solution were combined dried (MgSO₄) and concentrated in vacuo. The crude material was purified by crystallization in hot isopropanol (3 mL). to afford the desired product as a white solid (23 %); IR (KBr, cm $^{-1}$) 3297, 3078, 2928, 1635, 1559, 1363; 1 H NMR (DMSO + D₂O) 8.01 (t, J=5.3, 1H), 7.77 (d, J=7.2, 2H), 7.74 (s, 1H), 7.47 (m, 2H),

7.38-7.34 (m, 2H), 3.57 (br td, 2H), 3.35 (br td, 2H), 2.74 (s, 3H), 1.83 (s, 3H) ;
 LC/MS 95.4 % (220 nm), m/z (M +H⁺) 366.

Example 490

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To a solution of the compound of Example 9 (75 mg, 0.232 mmol) in ethanol (3 mL) at 23 °C was added N,N-diisopropylethylamine (38 µL, 0.417 mmol) and formamidine acetate (43 mg, 0.417 mmol). The reaction mixture was stirred at 23 °C for 18 h. Then, solvent was evaporated in vacuo and the crude material was purified by preparative HPLC using C18 column in acidic conditions to afford the TFA salt of the desired product as a light yellow solid (13 %); IR (KBr, cm⁻¹) 3420, 3058, 1683, 1652, 1559, 1436, 1203, 1131; ¹H NMR (DMSO + D₂O) 7.72-7.61 (m, 4H), 7.44-7.30 (m, 4H), 3.70-3.48 (br m, 4H), 2.69 (s, 3H); LC/MS 90 % (220 nm), m/z (M +H⁺) 351.

15

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Example 491



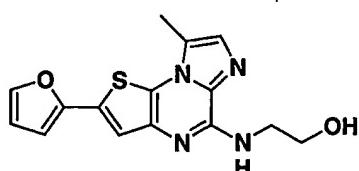
25

To 2-methyl-1-propanethiol (138 µL, 1.27 mmol) and KOH (89 mg, 1.59 mmol) in DMF (3 mL) was added compound 276G (95 mg, 0.318 mmol). The

reaction mixture was stirred at 75 °C in a sealed tube for six h. Then solvent was evaporated in vacuo and the crude material was purified on silicagel dry column using CH₂Cl₂ : MeOH (99:1) to (90:10) to afford compound 491 as an orange oil (10%); IR (KBr, cm⁻¹) 3377, 2956, 1559, 1540, 1404; ¹H NMR (MeOD) 7.34 (s, 1H), 7.31 (s, 1H), 3.84 (t, J=5.5, 2H), 3.72 (t, J=5.5, 2H), 2.81 (d, J=7.1, 2H), 2.74 (s, 3H), 1.89 (m, 1H), 1.06 (d, J=7.1, 6H); MS (⁷ESI, M + H⁺) m/z 337; HPLC: 90 % (220 nm); HRMS calcd for C₁₅H₂₀N₄OS₂: 337.1157; found 337.1155.

Example 492

10

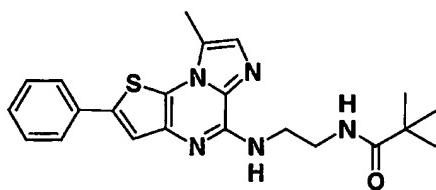


492

To compound 276G (85 mg, 0.26 mmol) in NMP (1.5 mL) was added 2-(tributylstannyl)furan (139 mg, 0.39 mmol), tris(dibenzylideneacetone)dipalladium (0) (24 mg, 0.026 mmol) and triphenylarsine (11.9 mg, 0.039 mmol). The reaction mixture was stirred at 90 °C in a sealed tube for four h. Then solvent was evaporated in vacuo and the crude material was purified on silicagel dry column using CH₂Cl₂ : MeOH (99:1) to (90:10) to afford compound 492 as a beige solid (24%); IR (KBr, cm⁻¹) 3361, 2977, 2919, 2853, 1558, 1540, 11360; ¹H NMR (DMSO) 7.76 (br s, 1H), 7.53 (s, 1H), 7.38 (s, 1H), 7.25 (t, J=5.5, 1H), 6.92 (d, J=4.1, 1H), 6.65 (m, 1H), 4.82 (br s, 1H), 3.64-3.55 (m, 4H), 2.72 (s, 3H); MS (⁷ESI, M + H⁺) m/z 337; HPLC: 93 % (220 nm); HRMS calcd for C₁₅H₁₄N₄O₂S: 315.0916; found 315.0911.

25

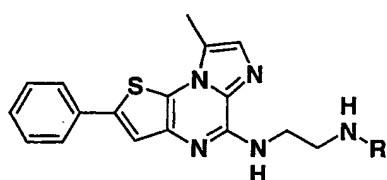
Example 493



250

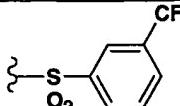
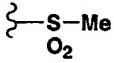
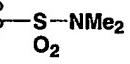
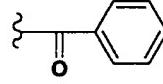
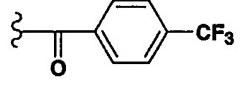
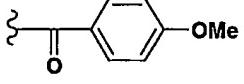
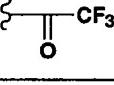
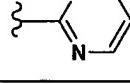
A solution of the compound of Example 9 (0.102g, 0.315 mmol) in tetrahydrofuran (3 mL) was treated with triethylamine (0.16 mL, 1.11 mmol) and 5 trimethylacetyl chloride (47 μ L, 0.38 mmol) at 0 °C. The reaction was stirred at room temperature for 1 h, then quenched with water and diluted with dichloromethane. The organic layer was washed with water and brine then dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography to give compound 493 (0.059 g, 46%); IR (KBr, cm^{-1}) 1636, 1560, 1540; ^1H NMR (DMSO-d6) 7.77-7.75 (m, 2H), 7.72 (s, 1H), 7.63 (m, 1H), 7.47-7.43 (m, 3H), 7.37-10 7.33 (m, 2H), 3.58-3.55 and 3.37-3.35 (m, 2H), 2.73 (s, 3H), 1.06 (s, 9H); MS ($^{\ddagger}\text{ESI}$, $\text{M} + \text{H}^+$) m/z 408; HPLC: 98 % (220 nm); HRMS calcd for $\text{C}_{22}\text{H}_{26}\text{N}_5\text{O}_1\text{S}_1$: 408.1858; found 408.1862.

15

Example 494-505

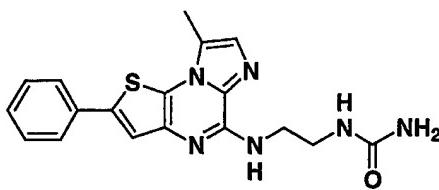
These compounds, where R is described in the table below, were prepared 20 from the compound of Example 9 according to the procedure described for Example 493.

Ex	R	HPLC Ret. time (min.) ^a	Purity %	MS (e/z) ($\text{M} + \text{H}^+$)
494		5.14	96	464
495		5.36	93	482

496		5.97	92	532
497		5.17	98	494
498		4.27	98	402
499		4.70	99	431
500		5.15	95	428
501		5.94	95	496
502		5.26	95	458.
503		5.22	98	420
504		4.44	99	395
505		4.10	90	402

Example 506

5

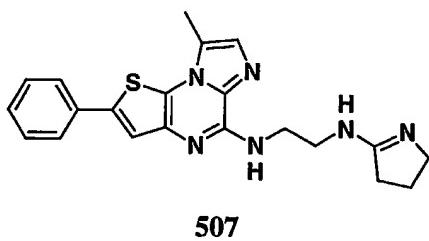


A solution of the compound of Example 9 (35 mg, 0.108 mmol) was dissolved in dry THF (1 ml) and trimethylsilyl isocyanate (44 μ l, 0.325 mmol) was added. The

reaction mixture was stirred in a sealed tube at 65 °C for 48 h. Then THF was evaporated in vacuo and the crude material was purified by preparative HPLC with a C18 column using NH₄OAc conditions to afford compound 506 as a light yellow glass.(22%); IR (KBr, cm⁻¹) 3412, 1683, 1653, 1559, 1429, 1202; ¹H NMR (MeOD) 5 7.74 (m, 2H), 7.67 (s, 1H), 7.52 (m, 1H), 7.44 (m, 3H), 3.76 (t, J=6.6, 2H), 3.51 (t, J=6.6, 2H), 2.85 (s, 3H), MS (^{+ESI}, M + H⁺) m/z 367; HPLC: 91 % (220 nm); HRMS calcd for C₁₈H₁₈N₆OS: 367.13411; found 367.13431.

Example 507

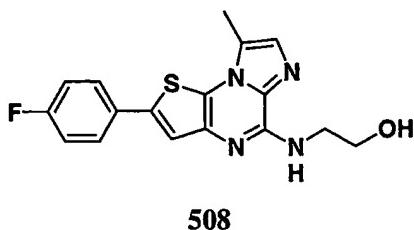
10



A solution of the compound of Example 9 (35 mg, 0.108 mmol) was dissolved
15 in DMSO (1 ml) and 5-ethoxy-3,4-dihydro-2H-pyrrole (122 mg, 1.08 mmol)
(Synthetic Comm. 18(14), pp 2625-1636 (1988)) was added. The reaction mixture
was stirred in a sealed tube at 95 °C for 48 h. Then, DMSO was evaporated in vacuo
and the crude material was purified by preparative HPLC with a C18 column using
TFA conditions to afford compound 507 as a light brown glass (50%); IR (KBr, cm⁻¹)
20 3202, 3064, 1683, 1430, 1200; ¹H NMR (MeOD) 7.78 (d, J=7.1, 2H), 7.59 (s, 1H),
7.49 (m, 3H), 7.41 (m, 1H), 3.93 (t, J=6.1, 2H), 3.80 (t, J=7, 2H), 3.68 (t, J=6.1, 2H),
2.89 (t, J=8.1, 2H), 2.85 (s, 3H), 2.25 (m, 2H); MS (^{+ESI}, M + H⁺) m/z 391; HPLC: 92
% (220 nm); HRMS calcd for C₂₁H₂₂N₆S: 391.17049; found 391.17128.

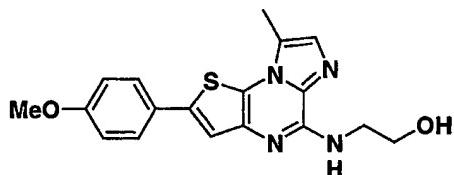
25

Example 508



5 A stirred solution of compound 276G (0.090 g, 0.28 mmoles) in N-methylpyrrolidinone (2 mL) was treated with tributyl-(4-fluoro-phenyl)-stannane (0.162 g, 0.42 mmol), tris-dibenzylideneacetone dipalladium (26 mg) and triphenylarsine (13 mg). The reaction was heated at 90 °C for 18 h. The cold mixture was placed on a SCX column, washed with MeOH and then with a 2M solution of 10 NH₃ in MeOH to recover the crude product. This crude material was purified by preparative HPLC with a C18 column to afford compound 508 as a yellow solid.(0.018 g, 19%); IR (KBr, cm⁻¹) 3358, 3182, 1552; ¹H NMR (DMSO-d6) 7.82-7.78 (m, 2H), 7.71 (s, 1H), 7.36 (s, 1H), 7.28 (t, J = 8.8, 2H), 7.21 (t, 1H), 4.81 (t,J=5.3, 1H), 3.64-3.61 and 3.58-3.56 (m, 2H), 3.68 (t,J=6.1, 2H), 2.72 (s, 3H); MS 15 (¹ESI, M + H⁺) m/z 343; HPLC: 100 % (220 nm); HRMS calcd for C₁₇H₁₆N₄O₁F₁S₁: 343.1029; found 343.1040.

Example 509

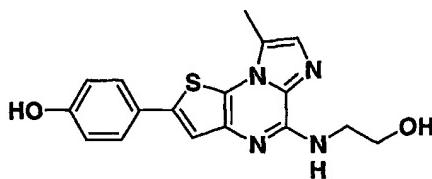


25 A stirred solution of compound 276 G (0.087 g, 0.27 mmoles) in N-methylpyrrolidinone (2 mL) was treated with tributyl-(4-methoxy-phenyl)-stannane (0.163 g, 0.41 mmol), tris-dibenzylideneacetone dipalladium (25 mg) and triphenylarsine (13 mg). The reaction was heated at 90 °C for 18 h. The cold mixture was placed on a SCX column, washed with MeOH and then with a 2M solution of

NH₃ in MeOH to recover the crude product. This crude material was purified by preparative HPLC with a C18 column to afford compound 509 as a white solid.(0.055 g, 57%); IR (KBr, cm ⁻¹) 3355, 1554, 1506, 1255; ¹H NMR (DMSO-d6) 7.68 (d, J = 8.8, 2H), 7.58 (s, 1H), 7.35 (s, 1H), 7.17 (t, J = 5.4, 1H), 7.01 (d, J = 8.8, 2H), 4.81 (t, J=5.3, 1H), 3.79 (s, 3H), 3.65-3.61 and 3.58-3.54 (m, 2H), 3.68 (s, 3H), 2.71 (s, 3H); MS (¹ESI, M + H⁺) m/z 355; HPLC: 100 % (220 nm); HRMS calcd for C₁₈H₁₉N₄O₂S₁: 355.1229; found 355.1233.

Example 510

10



510

15 A stirred solution of the compound of Example 509 (0.044 g, 0.124 mmoles) in dichloromethane (10 mL) at -78 °C was treated with a 1M solution of BBr₃ in dichloromethane (0.75 mL, 0.74 mmol) and the mixture was warmed to room temperature. After stirring for 4 hrs at room temperature, the reaction mixture was then cooled to -78 °C. MeOH (3 mL) was added and the mixture was warmed to
20 room temperature and concentrated. This crude material was purified by preparative HPLC with a C18 column to afford compound 510 as a yellow solid.(0.022 g, 52%); IR (KBr, cm ⁻¹) 3358, 3117, 1554, 1280; ¹H NMR (DMSO-d6) 9.72 (s, 1H), 7.56 (d, J = 8.6, 2H), 7.49 (s, 1H), 7.35 (s, 1H), 7.17 (s, 1H), 6.83 (d, J = 8.6, 2H), 4.80 (brs, 1H), 3.64-3.61 and 3.58-3.55 (m, 2H), 2.70 (s, 3H); MS (¹ESI, M + H⁺) m/z 341;
25 HPLC: 97 % (220 nm); HRMS calcd for C₁₇H₁₇N₄O₂S₁: 341.1072; found 341.1067.

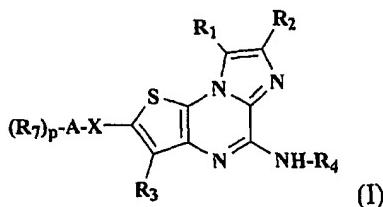
30

CLAIMS

We claim:

1. A compound of formula (I)

5



enantiomers, diastereomers, pharmaceutically-acceptable salts, and solvates thereof,
wherein

- 10 R₁, R₂, and R₃ are independently selected from hydrogen, halogen, alkyl, and
perfluoroalkyl;
- R₄ is -(CR₅R₆)_m-Z or -(cycloalkyl)-Z;
- R₅, R_{5a}, R₆ and R_{6a} at each occurrence are independently selected from hydrogen,
alkyl, substituted alkyl, amino, alkylamino, substituted alkylamino, hydroxy,
15 alkoxy, substituted alkoxy, cycloalkyl, heterocycle, aryl, and heteroaryl;
- R₇ at each occurrence is selected independently of each other R₇ from alkyl,
substituted alkyl, alkenyl, substituted alkenyl, halogen, cyano, -(CR_{5a}R_{6a})_q-OR_{8a},
-(CR_{5a}R_{6a})_q-SR_{8a}, -(CR_{5a}R_{6a})_q-SO₂R₁₀, -(CR_{5a}R_{6a})_q-NR₈R₉,
-(CR_{5a}R_{6a})_q-NR₈SO₂, -(CR_{5a}R_{6a})_q-NR₈SO₂R₁₀, -(CR_{5a}R_{6a})_q-SO₂NR₈R₉,
20 -(CR_{5a}R_{6a})_q-NR_{8a}C(=O)R_{9a}, -(CR_{5a}R_{6a})_q-NR_{8a}CO₂R_{9a}, -(CR_{5a}R_{6a})_q-C(=O)R_{8a},
-(CR_{5a}R_{6a})_q-CO₂R_{8a}, -(CR_{5a}R_{6a})_q-OC(=O)R_{8a}, -(CR_{5a}R_{6a})_q-C(=O)NR₈R₉,
-(CR_{5a}R_{6a})_q-CO₂NR₈R₉, -(CR_{5a}R_{6a})_q-OC(=O)NR₈R₉,
25 -(CR_{5a}R_{6a})_q-C(=O)NR_{8a}-NR₈R₉, -(CR_{5a}R_{6a})_q-C(=O)NR_{8a}SO₂R₁₀,
-(CR_{5a}R_{6a})_q-NR_{8a}C(=O)NR₈R₉, -(CR_{5a}R_{6a})_q-NR_{8a}SO₂NR₈R₉,
-(CR_{5a}R_{6a})_q-NR_{8a}C(=O)-C(=O)-NR₈R₉, -(CR_{5a}R_{6a})_q-NR_{8a}C(=O)-CO₂R_{9a},
-(CR_{5a}R_{6a})_q-N(SO₂R₁₀)(SO₂R_{10a}), -(CR_{5a}R_{6a})_q-OSO₂NR₈R₉, cycloalkyl,
(cycloalkyl)alkyl, heterocycle, (heterocyclo)alkyl, aryl, (aryl)alkyl, heteroaryl,

- and (heteroaryl)alkyl, or when A is heterocycle or cycloalkyl, one of R₇ may be keto (=O), and when A is a bond, then R₇ may be hydrogen;
- X is a bond, O, S, -NR₁₁-, -(CH₂)_n-, -CH=CH-, or -C≡C-;
- A is a bond, aryl, heteroaryl, heterocycle, or cycloalkyl;
- 5 Z is selected from hydrogen, methyl, OR₁₄, -C(=O)OR₁₄, -NR₁₂C(=O)R₁₃,
-NHC(=NR_{14a})R_{15a}, -NR₁₂CO₂R₁₃, -NR₁₂SO₂R₁₃, -C(=O)NR₁₄R₁₅, -NR₁₄R₁₅
and -NR₁₂-C(=O)NR₁₄R₁₅;
- R₈ R_{8a}, R₉ and R_{9a} are independently selected from hydrogen, alkyl, substituted alkyl,
alkenyl, substituted alkenyl, cycloalkyl, (cycloalkyl)alkyl, heterocycle,
10 (heterocyclo)alkyl, aryl, (aryl)alkyl, heteroaryl, and (heteroaryl)alkyl;
or R₈ and R₉ together with the nitrogen atom to which they are bonded may combine
to form a heterocyclo ring;
- R₁₀ and R_{10a} are independently alkyl, substituted alkyl, cycloalkyl, heterocycle, aryl, or
heteroaryl;
- 15 R₁₁ is hydrogen, alkyl, aminoalkyl, or hydroxyalkyl;
- R₁₂ is hydrogen or lower alkyl;
- R₁₃ is hydrogen, alkyl, substituted alkyl, cycloalkyl, heterocyclo, aryl or heteroaryl;
- R₁₄ R_{14a}, R₁₅ and R_{15a} are independently selected from hydrogen, alkyl, substituted
alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycle, (heterocyclo)alkyl, aryl,
20 (aryl)alkyl, heteroaryl, and (heteroaryl)alkyl;
- or R₁₄ and R₁₅ together with the nitrogen atom to which they are bonded may combine
to form a heterocyclo ring;
- m and q are independently 0, 1, 2, 3, 4, 5 or 6;
- n is 1 or 2; and
- 25 p is 0, 1, 2, 3 or 4, except when A is a bond, then p is 1.

2. A compound according to claim 1 wherein

R₁ is selected from hydrogen, halogen, and C₁₋₄alkyl;

R₂ is hydrogen;

30 R₃ is hydrogen or lower alkyl;

R₄ is -(CH₂)_m-Z;